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NEWS & FEATURES from NIH

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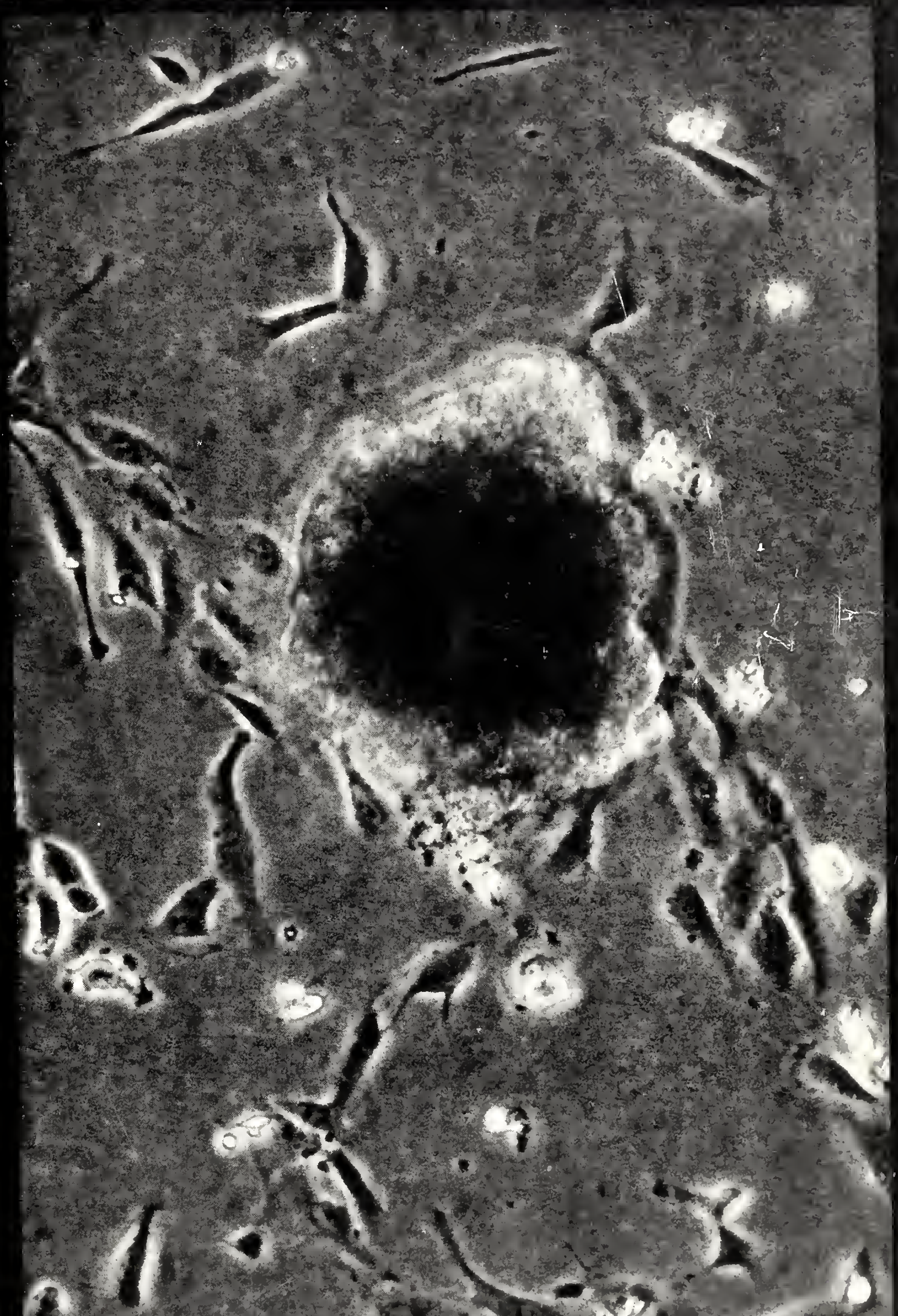

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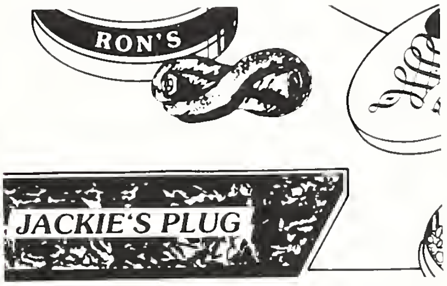
NINCDS-supported scientists are studying the origins of presbycusis—hearing loss in the elderly—to develop ways to prevent or reverse the impairment. Presbycusis, a Latin word for "old hearing", may be caused simply by the normal wear-and-tear of life or by certain medications, a genetic predisposition and cardiovascular problems. Although it cannot be treated, presbycusis can be ameliorated with the use of a hearing aid. In addition, the researchers believe that "prevention is the key" to minimizing the risks of hearing problems by avoiding loud and prolonged noise, and, for those over 55, by having a hearing checkup annually. See page 5.

About 9000 Americans die each year from oral cancer. Some of these cases may be attributed to the long-term use of smokeless tobacco, such as snuff and chewing tobacco. Recent evidence indicates that the use of smokeless tobacco in this country is rising. In an NCI study, epidemiologists found that the high risk of oral cancer among southern women was definitely associated with the use of smokeless tobacco and could not be explained by any other risk factors, including cigarette smoking. Certain types of nitrosamines—known to have a clear association with human cancer—have been found in smokeless tobacco. In addition, research indicates, that smokeless tobacco users may be exposed to even greater amounts of carcinogenic agents than cigarette smokers. See page 2.



Fecal incontinence the inability to control bowel movements has been neglected or overlooked by those caring for the elderly. Most cases occur among the elderly, but are due to neurological and medical problems that can occur at any age. Now, psychologists at the National Institute on Aging's (NIA) Gerontology Research Center (GRC) and the Johns Hopkins School of Medicine have shown that biofeedback, in conjunction with certain exercises, can eliminate or reduce the problem in otherwise healthy adults. Almost all of the 13 subjects studied benefited significantly from this approach to their problem. The investigators suggest that their method has potential for enhancing the lives of thousands of elderly people who suffer from this disorder. See page 7.

Recent scientific evidence indicates that healthy women who exercised before pregnancy can continue to exercise during pregnancy without causing harm to themselves or to their fetuses. A study supported by the National Institute of Child Health and Human Development (NICHD) involved examining women's responses to two types of exercise performed during the last eight weeks of their pregnancies. They concluded that exercise is safe, if a woman has exercised before pregnancy. However, no exercise standards have been set for pregnant women, and, if a woman has never exercised before, then, the researchers conclude, she shouldn't start exercising when pregnant. See page 8.

Smokeless Tobacco Use—On the Rise—and Linked with Oral Cancer

Carol Trotman

The use of smokeless tobacco products—chewing tobacco and snuff— has been linked to cancers of the mouth and throat and to other health problems, like gum disease, tooth loss, increased blood pressure, and oral leukoplakia, a precancerous condition. Currently, about 9,000 Americans per year die from oral cancer. Oral cancer accounts for about 4 percent of all cancers that occur in the United States each year.

The 1982 report of the Surgeon General notes that long-term use of snuff "appears to be a factor in the development of cancers of the oral cavity, particularly cancer of the cheek and gum." In 1984, the International Agency for Research on Cancer (IARC) concluded that smokeless tobacco products are cancer-causing agents. The organization stated that there is "sufficient evidence that oral use of snuffs of the types commonly used in North America and Western Europe is carcinogenic to humans. ("Sufficient evidence" of carcinogenicity, as defined by IARC, indicates "that there is a causal relationship between the exposure and human cancer.") There is limited evidence that chewing tobacco of the types commonly used in these areas is carcinogenic. Epidemiological studies that did not distinguish between chewing tobacco and snuff provide sufficient evidence for the carcinogenicity of oral use of smokeless tobacco products."

There is evidence that the use of smokeless tobacco in the United States is increasing. As recently as 1975, fewer than 3 percent of adult males used snuff and fewer than 5 percent used chewing tobacco. Rates for females were even lower with 1.3 percent using snuff and 0.6 percent using chewing tobacco. Between 1970 and 1979, however, production and sales of fine cut tobacco, used in moist snuff, increased 188 percent, and increases in moist snuff production have continued at the average rate of 8 percent each year.

Current national prevalence figures are not yet available, but a number of local and regional surveys conducted in different areas of the country have shown dramatic increases in use of smokeless tobacco, especially snuff, by adolescents and children. In many areas 20 to 40 percent of adolescent males have tried these products, and in some regions this figure is much higher. Increased use coincides with aggressive advertising campaigns that primarily target young adults.

NIH's National Cancer Institute and the National Institute of Dental Research will be sponsoring a consensus conference this winter on Health Implications of Smokeless Tobacco. Their findings will be published later in the year. (See box on the following page) NIH Photo 2106

By chewing or dipping, smokeless tobacco users can rapidly achieve nicotine levels comparable to or higher than those of smokers. This poses the danger that use of these products may lead to nicotine dependence and thereby encourage cigarette smoking, which constitutes an even greater health risk.

Chewing tobacco in the United States comes in three forms—plug, twist, or loose-leaf. The tobacco can be plain or flavored. Plug chewing tobacco is made of stemless tobacco leaves and flavoring agents that have been pressed into cakes. A portion of the cake is bitten off and held in the mouth or chewed for several hours. Stemless tobacco leaves can also be twisted and folded to make twist tobacco or the leaves can be shredded to irregular fragments or flakes to make loose-leaf chewing tobacco.

Snuff is powdered tobacco that can be dry or moist, coarse or fine. This product is often toasted and various combinations of flavorings, sweeteners, and scents can be added. In Britain, it is sniffed through the nose. In the United States and Scandinavian countries, snuff is put in the mouth or "dipped." A small portion or "pinch" of a finely ground tobacco is placed in the mouth and held between the lip and gum or cheek and gum.

Tobacco chewing is common among residents of areas with high incidences of oral cancer. India has high rates of mouth and throat cancer, about 75 percent of these oral cancer cases can be attributed to tobacco habits. In India, street vendors sell "pan"—a mixture of betel leaves and nuts, tobacco and lime—or "khaini"—a mixture of tobacco and lime.

A similar combination of betel or tobacco leaf, ash, lime, cotton, sesame and other ingredients, called "nass," is used in certain Soviet republics and parts of Afghanistan. Oral cancer is also high in these areas as well as parts of southeast Asia and the Pacific Islands. Other areas of the world with high oral cancer incidence and mortality include Puerto Rico, Brazil, southeastern parts of the United States, France, and Hong Kong.

Using cancer maps that show the geographic distribution of deaths from cancer, epidemiologists from the Division of Cancer Etiology at the National Cancer Institute (NCI) noted that oral cancer death rates were excessively high for white women in the southeastern United States. These death rates in the southeast of the United States exceeded corresponding rates in the north by 30 percent in urban areas and 90 percent in rural areas.

NCI epidemiologists began a study of women in North Carolina to determine what factors could be associated with the higher rates of oral cancer that were indicated on the cancer maps. Risk factors associated with oral cancer are: the use of tobacco, including snuff, chewing tobacco, cigarettes, or pipes; alcohol consumption; low socioeconomic status; occupation; nutritional deficiences; and poor dentition. Researchers considered these factors while evaluating the relationship of smokeless tobacco products to oral cancer.

In 1981, the researchers published the results of the case-control study that compared 232 North Carolina women with oral and pharyngeal cancers to 410 women of similar age and background without these cancers. Forty-six percent of the women with oral or pharyngeal cancer had used snuff. Snuff users were four times more likely than non-users to develop oral or pharyngeal cancer and the risk for cancers of the cheek or gum increased to 50-fold for long-term snuff users. The study concluded that the high risk of oral cancer among southern women was definitely associated with smokeless tobacco use and could not be explained by any of the other risk factors, including cigarette smoking.

In the Third National Cancer Survey of 1969 to 1971, NCI researchers looked at the effect of tobacco, alcohol, and socioeconomic status on cancer patients. Men who frequently used smokeless tobacco for many years were seven times more likely to develop mouth or gum cancer, excluding tongue cancer, than non-users. The moderate users—both men and women—were four times more likely than non-users to develop the same cancers.

Oral cancers usually appear at the site most often in contact with the tobacco. In a 1963 study in Tennesee, researchers found that 90 percent of 159 women with cancer of the cheek and gums (where snuff is usually placed) used snuff. In contrast, only 22 percent of 55 women with cancer of other parts of the mouth, for example, the tongue and floor of the mouth, dipped snuff. Researchers also reported an ear cancer in a Minnesota farmer who placed snuff in his ear for 42 years.

Researchers have found that oral leukoplakia is more common among smokeless tobacco users than persons who do not have the habit. A likely possible forerunner to cancer, oral leukoplakias are white, thickened patches on the mucous membranes of the lip, cheeks, gums, or tongue. These patches, which cannot be scraped off and often must be removed by surgery, can develop into cancer. The patches sometimes disappear when an individual stops using smokeless tobacco.

Current treatment methods for oral cancer include surgery, radiation therapy, and chemotherapy. Patients with oral cancer may be disfigured or have functional problems due to their treatment. Researchers have also shown that patients with oral cancer have a greater chance of developing cancer of the pharynx, larynx, and lung.

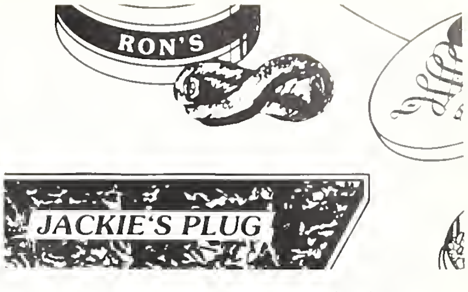
Other untoward health effects of smokeless tobacco use include increased blood pressure and heart rate, bad breath, discolored teeth, gum disease, and early tooth loss.

Tobacco-specific N'-nitrosamines (TSNA) are formed from nicotine and from other tobacco alkaloids during aging, curing, fermentation and processing of tobacco. Nicotine and other alkaloids, which are addictive and are the main reason for the tobacco user's habit, are readily absorbed through the mucous membranes.

Scientists have isolated N'-nitrosonornicotine (NNN), one of the N'-nitrosamines, in chewing tobacco, snuff, cigarette and cigar tobaccos, and mainstream cigarette smoke. NNN and other N'-nitrosamines cause cancers of the esophagus, nasal cavity, windpipe, and lung in laboratory animals. According to these scientists, "Hardly any other group of compounds occurring in the non-occupational environment has been more clearly associated with human cancer than the tobacco specific N'-nitrosamines. . . ."

These substances have been identified in snuff and fine-cut chewing tobacco at levels far higher than in tobaccos used for other purposes. The highest levels of environmental nitrosamines, or NNN, are found in unburned commercial United States' tobacco products at levels of 2 to 90 parts per million (ppm). The 1982 report of the Surgeon General notes that studies of popular snuff tobaccos from the United States, Denmark, Germany, and Sweden showed 5.5 to 106 ppm of TSNA in these materials, the highest levels of carcinogenic nitrosamines reported in a consumer product that is taken into the body.

Additional NNN can be formed during chewing by the reaction of nitrites in saliva with nicotine in the tobacco. Researchers reported that the amount of NNN in fine-cut chewing tobacco increased by 44 percent when mixed with saliva. Researchers also compared the amount of NNN in a mixture of tobacco and saliva with that contained in mainstream smoke from a typical non-filter cigarette and found 1,000 times more NNN in the tobacco-saliva mixture than in the mainstream smoke. This indicates that smokeless tobacco users may be exposed to even greater amounts of carcinogenic agents than cigarette smokers.



The amount of N'-nitrosamines in tobacco also increases as the product ages in the open air. Researchers have found a 50 percent increase in N'-nitrosamines in snuff samples that were exposed to air for two weeks. New methods for tobacco processing and airtight wrapping of individual portions may reduce the concentrations of nitrosamines in these products.

Many smokeless tobacco users are young people who may experience deleterious health effects from long-term snuff use or may try other forms of tobacco. For these reasons, NCI's Division of Cancer Prevention and Control is developing intervention programs to reduce smokeless tobacco use among all users, especially young people. ■

The National Institutes of Health will hold a Consensus Development Conference on the Health Implications of Smokeless Tobacco Use, January 13-15, in Masur Auditorium, the Clinical Center, on the NIH campus. There is no registration fee for the meeting, which is open to the public.

In the United States the use of chewing tobacco and snuff appears to be increasing, especially among children and adolescents. Serious questions have been raised regarding health and behavioral effects from the use of smokeless tobacco products. Among the key questions to be addressed at this conference are whether smokeless tobacco use increases the risk of oral and other cancers and periodontal disease.

The meeting is sponsored by the National Cancer Institute, the National Institute of Dental Research, and the NIH Office of Medical Applications of Research. To register and obtain further information about the meeting, call Michael Bernstein, 496-1143 or Joyce Doherty, 496-6641.

NIADDK Conference Provides Scientists with Insights Into the Use of Cell/Tissue Culture in Kidney Research

Jim Fordham

New insights into the use of cell and tissue culture technology in the exploration of the physiology and pathophysiology of the kidney were the focus of a conference sponsored recently by the Division of Kidney, Urologic, and Hematologic Diseases (KUH), National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK).

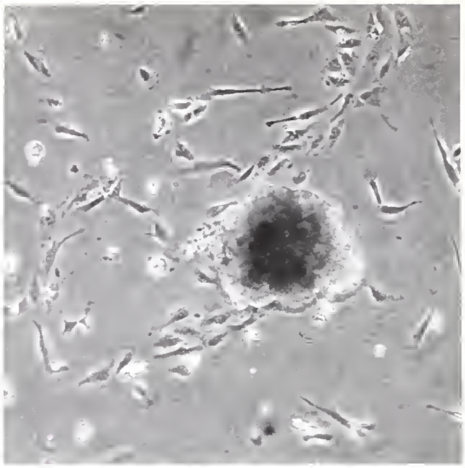
Dr. Gary E. Striker, Director of the KUH Division welcomed about 200 scientists from across the U.S. and abroad. He said the specialty of nephrology (study of the kidney) is evolving rapidly on the basis of new technologies being introduced, principally those of cellular biology and molecular biology.

"This field," said Dr. Striker, "is poised on the brink of investigating many events at the cellular level that had previously been studied at the whole organ or the individual nephron (kidney cell) level."

Dr. Jeffrey I. Kreisberg, Associate Professor of Pathology and Medicine at the University of Texas Health Science Center at San Antonio, discussed the contractile properties of glomerular mesangial cells. He said study of the substances that regulate contraction of these cells is important "because it seems that in many disease states, the contractile properties of mesangial cells (the thin membrane that supports the capillaries in the glomerulus) are altered, and this leads to marked alterations in blood flow through the glomerulus (capillaries that filter waste from the blood) that can damage fragile glomerular structures."

Dr. Darwin Prockop, Professor of Biochemistry, Rutgers Medical School, Piscataway, discussed mutations that occur in collagen genes and their consequences in man. He described how certain small changes in the gene or the DNA lead to major alterations in various proteins that, in some instances, are lethal to human beings. He suggested that some day many of the diseases scientists are now studying in tissue culture will be studied at the level of the gene or the DNA to find various mutations that might explain the disease symptomatology.

"This shows" Dr. Kreisberg said, "that we must understand in normal cells, as well as in cells that are altered due to various genetic or other diseases, how genetic material controls the expression of cell function. We talked throughout these lectures about transport properties of cells, about the contractile properties of cells, and how these various properties might be modulated.



A glomerulus of a human kidney in culture (magnified 100 times), showing individual glomerular cells migrating from it.
This photo is from the laboratory of Dr. Liliane Striker, NIADDK, whose group is studying cellular mechanisms in human kidney diseases.
NIH Photo 2107

But it will be of great interest in the future to perhaps find out which gene in the nucleus of cells controls the various functions of a particular cell. I think we might find out that in various diseases, the alteration in function that we have been describing that takes place in various cell types can be traced back to the gene, and mutations or alterations that take place in DNA lead to an alteration in function of cells."

Several studies were presented describing ways the cell in tissue culture is being used to improve understanding of the physiology and pathophysiology of the renal glomerulus. Dr. Peter A. Ward, Professor of Pathology at the University of Michigan Medical School, Ann Arbor, delivered a state-of-the-art presentation on the inflammatory response in the glomerulus. Dr. Ward described mediators of inflammation, known as free radicals, that are released by the blood cells. He discussed the implications of the formation of these mediators and the inflammatory response in body organs generally.

Dr. Morris J. Karnovsky, Professor of Pathological Anatomy at the Harvard Medical School, presented an overview of techniques to culture and to modulate the growth of glomerular cells. He said that heparin, a potent anti-coagulant, can modulate the growth of mesangial cells, and pointed to the eventual use of compounds similar to heparin to control growth of these cells, which proliferate in many disease states. The growth regulatory effects of heparin, Dr. Karnovsky emphasized, are independent of its anti-coagulant effects.

Dr. Giuseppe A. Andres, Professor of Pathology, State University of New York at Buffalo, described studies of the role of intrinsic cell surface antigens in the formation of immune deposits. He and his colleagues used cultured glomerular epithelial cells to demonstrate that antigens to which immunoglobulins (antibodies) are made in disease states are normally present on the surface of these cells. The researchers are able to modulate these antigens so that they do not react with the antibodies, or if a reaction does occur, it is controlled so that pathology does not develop.

Dr. Ellis D. Avener, Assistant Professor of Pediatrics at the Children's Hospital of Pittsburgh, presented a model developed by his group in which metanephric organ tissue (tissue from developing kidneys) is studied in culture. Cysts were induced in metanephric culture by manipulating the medium levels of various glucocorticoid hormones. The investigators hope that if they can discover the mechanism by which the hormones induce cyst development, they may be closer to the prevention or control of polycystic renal disease in humans.

Dr. Dorie W. Schwertz, Assistant Professor of Pharmacology at the University of Illinois College of Medicine, Chicago, reported on the nephrotoxic effects of gentamicin (an antibiotic commonly used to treat infections). The investigators found that gentamicin and other aminoglycosides induce damage to LLC-PK$_1$ cell membranes, resulting in marked cell injury and eventual cell death. LLC-PK$_1$cells are an epithelial line from the kidney.

Energy metabolism and cell survival in cultured LLC-PK$_1$ cells were discussed by Dr. Manjeri Venkatachalam, Professor of Pathology and Medicine at the University of Texas Health Science Center, San Antonio. Dr. Venkatachalam described the effects of adenosine triphosphate (ATP) depletion on these cells and the resultant membrane changes.

Calcium homeostasis in LLC-PK$_1$ cells and in glomerular mesangial cells was discussed by Dr. Joseph V. Bonventre, Assistant Professor of Medicine at the Harvard Medical School. He described the use of newly developed techniques to explore how the level of calcium inside the cell is regulated and compartmentalized by the internal cell organelles.

Dr. Richard C. Boucher, Professor of Medicine at the University of North Carolina at Chapel Hill, described research in which he and his colleagues studied the transport properties of cultured respiratory epithelia from patients with cystic fibrosis. The researchers designed a cell culture system for human respiratory epithelia and adapted a series of techniques to investigate the ion transport activities of cultured cells.

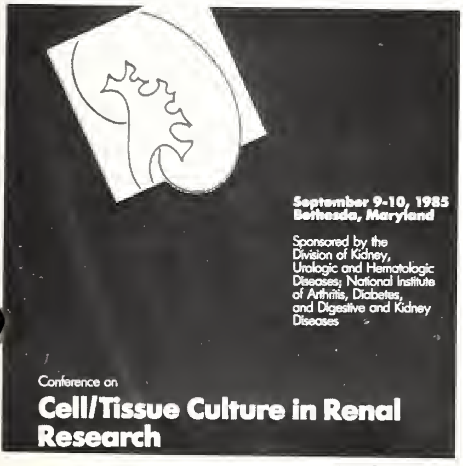
Speaking of the vital importance of new cell culture technology, Dr. Kreisberg said: "In the past, we would rely on either looking at cell function through looking at the whole animal, or looking at an isolated organ, and in fact even looking at isolated tubules. With all the previous techniques, one always had in the back of one's mind: 'What else in the blood is having an effect on this experiment?' With the use of cell culture, one is able to isolate a particular part of the kidney that one wants to study in culture and in some cases under conditions where no proteins are present, and one can then manipulate the environment of the cells and therefore study directly what is happening to cell function.

"This has great implications for future research as one can see from these meetings. As the technology gets better and better, we will be able to get pure cultures of cells from all nephron segments and study their normal function—exactly what turns on a particular cell type to perform a vital function that it has to do. Once we understand the mechanisms of normal cell function, then we can see what happens to cells when they are altered.

"Many investigators are doing animal and organ types of experiments who, if they were aware of the methodology now available to grow particular cells that they may be interested in, could make their experiments more focused and well-defined, and get more precise answers."

"It is quite likely," said Dr. Striker, "that both cell-cell interaction and extracellular milieu-intracellular milieu interactions can now be studied at a much more sophisticated level. Investigations at this level will help us to understand both the function of individual cells and the organ itself. This kind of understanding is essential to the interpretation of the role of renal function in overall body homeostasis and in numerous disease states."

Dr. Dennis A. Ausiello, Associate Professor of Medicine at the Harvard Medical School, seemed to express the feeling of many of the participants that: "Nephrology has reached a turning point in the last half dozen years with increased use of cell biology and molecular biology techniques. This meeting has summarized research being conducted around this country and around the world, and has provided insights for many new studies." ■



September 9-10, 1985
Bethesda, Maryland

Sponsored by the Division of Kidney, Urologic and Hematologic Diseases; National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

Conference on

Cell/Tissue Culture in Renal Research

NIH Photo 2108

Research on Presbycusis Focuses Attention on Hearing Impairment

Kate Callen

A common ailment with an uncommon name, hearing loss associated with aging afflicts at least one in four elderly people. Research on "presbycusis" supported by the National Institutes of Health has linked the disorder to Western civilization, certain medications, genetic predisposition, and cardiovascular problems.

The third most prevalent chronic impairment among elderly people is *presbycusis*, a Latin word that means "old hearing." The stereotype that says older people tend to be hard of hearing is unfortunately all too true: according to national health surveys, at least 40 percent of all Americans 65 and older suffer some degree of hearing loss.

With support from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the focal point within the Federal Government for research on hearing, scientists have found that gender and race may play a role in presbycusis—and that promising new hearing aid technologies may alleviate this handicap.

According to Dr. Ralph Naunton, Director of the NINCDS Communicative Disorders Program, presbycusis is becoming a serious health problem in the United States for two reasons:

—"As medical care improves and people live longer," Dr. Naunton explains, "the Nation's elderly population will grow larger," and more people will be afflicted with presbycusis. In 1980, 10.2 million older Americans were hearing impaired. By the year 2000, the number will rise to 14 million.

—Undetected hearing loss is often mistaken for mental confusion. Family and friends who don't know that Grandpa can't *hear* what's being said may assume that he can no longer *comprehend*— and Grandpa is left out of future conversation.

Scientists funded by NINCDS are trying to discover the origin of presbycusis and develop ways to prevent or reverse the impairment. In particular, Dr. Naunton reports, "fundamental studies of hearing and hearing impairment have led us to the threshold of dramatic improvements in hearing aid technology."

What causes presbycusis? Evidence to date suggests that, by age 65, the inner ear and the auditory nerve may simply be showing signs of normal wear-and-tear. The structures most prone to aging or wear (specifically, the hair cells) govern the ability to hear high-pitched sounds and are characteristically most affected by presbycusis. People often quip that "the elderly can hear what they want to hear." In fact, Dr. Naunton points out, many older people cannot hear high-pitched or high-frequency sounds but can still discern low, well-modulated tones.

The elderly with presbycusis are encouraged to use a hearing aid to restore human contact and enhance the quality of life. Improved technology may eventually produce hearing aids that are sensitive to the higher frequencies that presbycusis patients miss. NIH Photo 2109

Presbycusis may also result from changes in the blood supply to the ear following heart disease, high blood pressure, or other circulatory problems—and indeed, studies have linked hearing loss with both diabetes and cardiovascular disease, two disorders that particularly affect older people.

The older ear also pays the price for a lifetime of exposure to all kinds of loud noise, says Dr. Naunton. In a sense, he notes, "presbycusis may be a byproduct of Western civilization." The Mabaan people in the African Sudan, as one example, are believed to have excellent hearing in old age—and the Mabaan environment is exceptionally quiet by Western standards.

The cumulative effects of medications, another suspected cause of hearing loss, may pose a special threat to the elderly, says Dr. Naunton, because people age 65 and over represent 11 percent of the population but use 25 percent of all prescription drugs. Research has drawn correlations between hearing loss and use of certain antibiotics that are prescribed in life-threatening situations, certain diuretics, antitumor agents, and aspirin—all drugs that are widely used by elderly patients. A regular dosage of eight aspirin a day, not uncommon as a treatment for arthritis, can provoke temporary hearing loss and may result in residual damage to the ear.

Genetics also may play a role; some individuals inherit a predisposition for hearing problems. In fact, Dr. Naunton reports, symptoms of presbycusis can appear by age 40 or even earlier. Caucasians are more prone to presbycusis than other races, and blacks seem to be resistant (one theory is that blacks have relatively large ear canals which help protect the inner ear against the damaging effects of loud noise). Before age 65, men show a higher prevalence of hearing problems than women; after 65, presbycusis rates for both sexes are about the same. Dr. Naunton believes that the earlier gender gap occurs because more men than women are exposed to occupational and recreational noise.

Presbycusis cannot be treated as yet, but, with existing technology, hearing aids can help to some extent. "The elderly with presbycusis often are encouraged to use hearing aids because this will help restore human contact and enhance the quality of life," Dr. Naunton says. "In fact, this is not enough: the elderly should be encouraged to use hearing aids early in order to *prevent* loss of human contact and *prevent* diminution of the quality of life.

"Hearing aids may not be perfect," he continues, "but even a less-than-perfect aid will be worth its weight in gold if it will prevent loss of contact with family and friends."

Future prospects for improved hearing aids are very good, according to Dr. Naunton. For one thing, he says," our scientists are examining how information travels from the inner ear to the brain, and their findings should help us develop better hearing aid technologies."

Two developments in hearing aid research are particularly exciting, in Dr. Naunton's view. The first is the "say-it-again" hearing aid; like the black box in airplane cockpits, this device will continually record what is said and, on command, will play back the last thing recorded. The second device is the tiny but high-fidelity electric microphone that is being used in "directional" hearing aids to help a person focus in on desired sounds and screen out background noise.

Some hearing aid advances will be made possible by computerized or digital circuitry (the same technology responsible for the chronograph/alarm/calendar digital wrist-watches). Dr. Naunton estimates that digital hearing aids will be on the market in 5 to 10 years. He expects that early digital models will be larger (but much more versatile) than the current analog devices, and eventually, the new technology will produce scaled-down aids designed for each wearer's specific needs. These models might be more sensitive to the higher frequencies that presbycusic patients miss.

For now, however, "prevention is the key," Dr. Naunton emphasizes. People of all ages should minimize the risks of hearing problems by avoiding loud and prolonged noise. Ground crews at airports have long worn ear protectors on the job, and other workers in noisy settings, like steel mill operators and rock musicians, are doing the same. Such protectors, or even earplugs, should be used around common household noises (e.g., lawnmowers and vacuum cleaners) because these can damage the ears over time.

Dr. Donald Morgan, UCLA researcher, under a grant from NINCDS, tests the hearing of a patien participating in hearing loss studies. NIH Photo 2110

The Institute also recommends that all people over age 55 have a hearing checkup once a year, a simple office procedure that can be conducted by an audiologist (a hearing expert) or an otologist (a physician who specializes in hearing). Local hearing associations can recommend such professionals.

Regular tests are the only reliable means of early diagnosis, says Dr. Naunton, because of the peculiar nature of presbycusis: while other types of hearing loss tend to occur rather more quickly and often affect only one ear, hearing impairment associated with aging is gradual and diminishes sound in both ears, making it harder to detect. Some telltale signs of presbycusis are tinnitus (a ringing in the ears), repeated asking of the question "What did you say?", and a tendency to turn up the volume of the television set.

Unfortunately, many elderly persons may resent suggestions to have their hearing checked because, says Dr. Naunton, "society has come to view hearing loss in later years as a confirmation o 'senility' and a link with mental impairment—just as the word 'dumb' has an adverse dual meaning." If an elderly relative or friend seems to be having trouble hearing, suggest a visit to the family physician. "Try to gain their confidence," Dr Naunton advises," and don't get exasperated."

The elderly person who is diagnosed as having presbycusis especially needs patience and consideration. "Work at communicating with them," Dr. Naunton urges. "There's no need to shout; just raise your voice a little. Learn to speak clearly and slowly, and enunciate consonants. Face the person as you're talking so he or she can lip-read. You know, we all unconsciously do a certain amount o lip-reading during conversation, and many people with presbycusis have benefited greatly from lip-reading courses.

"Verbal communication is our chief means of interacting with other people," Dr. Naunton continues. "Without sound, we're deprived of essential human contact." To enhance the quality of life for older Americans, NINCDS will continue to study the problem of presbycusis, to bring it to public attention, and to help the elderly get the care they need. ■

Biofeedback Proves Useful for Treating Fecal ncontinence in the lderly

lan Ehrman

Operant conditioning, or biofeedback, can significantly decrease episodes of bowel incontinence in most otherwise healthy, elderly individuals. This finding is based on an in-depth study recently conducted by investigators at the National nstitute on Aging's (NIA) Gerontology Research Center (GRC) and the Johns Hopkins School of Medicine.

For too long now, the problem of fecal ncontinence, the inability to control bowel movements, has been either negected or overlooked by physicians and by society in general. In the past, it was onsidered by some as concomitant with ging in later life. And, although its incidence does increase with advancing ge, most cases are now recognized as being due to neurological and other medcal problems which can occur at any ge.

According to the National Center for Health Statistics, about 30 percent of ursing home residents suffer from this ondition. A recently completed survey of 955 persons aged 60 or older (MESA ging Survey at Washtenaw County, chigan, principal investigator, A Diokno, M.D.) shows that the prevalence f fecal incontinence in community-welling elderly people is 7.2 percent.

There exist a number of medical and motional problems that may increase he likelihood of fecal incontinence. For stance, an injury to the spinal cord can licit a loss of control over excretory funcons. Anal surgery may do the same. Seile dementia or cerebrovascular accients (strokes) can also be contributing actors, since patients with gross intellecual impairment may be unable to control hose muscles that normally preserve ontinence.

Also, anxiety, depression, and other sychological factors may be related to he onset and duration of symptoms. However, these psychological symptoms ould be the result of the patient's inconnent status rather than actual causes, ome experts believe.

In addition to the increased risk of ladder infection in women and skin disase for both sexes which may result om bowel incontinence, the condition an be embarassing and emotionally disurbing. The constant fear of soiling can ause the patient to fully withdraw from ose around him. This, in turn, can lead isolation, as well as a neglect or disreard for appropriate medical treatment. Now, however, psychologists Drs. William Whitehead, Kathryn Burgio, and Bernard . Engel of the GRC and the Johns Hopkins School of Medicine have demonstrated that biofeedback, when used in conjunction with anal sphincter-strengthening exercises, can eliminate or effectively reduce soiling episodes in many othewise healthy, older adults.

The investigators reported their findings in a recent issue of the *Journal of the American Geriatrics Society*. Initially, they worked with 18 fecally incontinent (one incident or more per month) patients, aged 65-92, treating them for constipation as a possible cause of their bowel problems. Most patients were at least somewhat ambulatory, however, three were wheelchair-bound.

Following complete diagnostic evaluations, two patients were found to exhibit symptoms characteristic of senile dementia, while one was unable to sense rectal distention. These three subjects were excluded from further study. Habit training, that is, programmed attempts to defecate each day immediately after breakfast, worked well in preserving continence for two patients; they did not need to take the next step—sphincter-biofeedback training.

The remaining thirteen patients, all of whom did not benefit from habit training, or sphincter-strengthening activities, *per se*, were placed on a biofeedback program. In general, this involved teaching each patient how to contract the anal muscles at proper times to prevent soiling. Three balloons were inserted into the anus—one to the rectum and one each to the internal and external sphincters. A brief pulse of air inflated the rectal balloon, mimicking the actions of a stool.

Meanwhile, patients were instructed to watch a polygraph tracing, which indicated whether or not they were emitting the proper muscular responses. Also, patients relied on verbal reinforcement from the instructor when the correct response was made. They were similarly informed when they responded inappropriately.

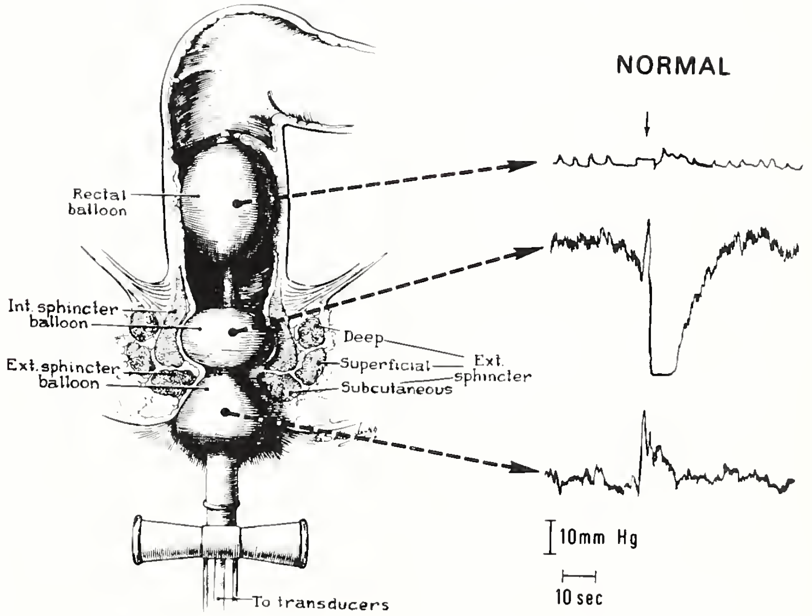
The 13 subjects underwent the biofeedback therapy once every two weeks during 45-minute sessions. In addition, they practiced exercising their sphincter muscles repeatedly. This protocol continued until the subjects experienced fewer than one incontinent event per month, or until they failed to show symptomatic improvement after two consecutive visits. Family members assisted the patients in recording bathroom-related activities.

The results of this training indicated that almost all 13 subjects benefited significantly. Six subjects succeeded in reducing their frequency of accidents to less than one per month. Another four patients witnessed a 75 percent reduction in soiling incidents. Follow-ups indicated that five patients remained fully continent for periods of up to one year following treatment.

This study also showed that simply instructing patients to exercise their anal sphincter muscles without providing biofeedback training was not sufficient. Patients who were instructed to perform these exercises without biofeedback did not show significant gains in muscle strength or continence. However, both muscle strength and continence improved when biofeedback was introduced.

Additionally, the procedure proved cost-effective. On the average, each subject required only four 45-minute sessions to demonstrate proficiency of bowel control, thereby improving his or her clinical status.

The investigators suggest that this therapeutic approach has widespread potential for enhancing the lives of thousands of older men and women afflicted by fecal incontinence, both in nursing homes and in the community-at-large. ■



A balloon is placed in the rectum and records rectal and sphincteric responses to air pressure

NIH Photo 2111

Research Shows that Pregnant Women Can Safely Continue to Exercise

Patricia Blessing

Because of the increasing popularity of exercise among women—about half of all women exercise regularly—many are continuing to exercise when they become pregnant. Most physicians agree that healthy women who exercised regularly before pregnancy can carry themselves and their fetuses safely to term while continuing to exercise.

Still, no exercise standards for pregnant women have been set. Only a handful of studies in humans have explored the possible benefits or risks to the mother and fetus.

"Because the exercise phenomenon is relatively new, human studies on the effects of exercise during pregnancy are in short supply," said Jean-Claude Veille, M.D., an obstetrician at Case Western Reserve University and a National Institute of Child Health and Human Development (NICHD) grantee. But some of the questions about the safety of exercising during pregnancy are beginning to be answered.

Dr. Veille and his colleagues recently conducted a study in pregnant women to see what effect, if any, moderate exercise had on the uterus. The muscle of the uterus contracts irregularly during pregnancy, causing the abdomen to harden periodically in preparation for labor. But the amount of uterine activity concerned the researchers because, although some activity during pregnancy is normal, excessive uterine activity may lead to early labor.

But the results were reassuring. "None of the women had any increase in uterine activity," Dr. Veille said. He added that "exercise itself did not trigger premature labor in these healthy women."

Dr. Veille's conclusions come after studying 17 women's responses to two types of exercise performed during the last eight weeks of their pregnancies. The women either walked for 30 minutes or pedaled a stationary bicycle for 15 minutes. All of the women were healthy and participated in a regular exercise program before the experiment began.

The researchers measured uterine activity with a device called an external tocometer, which is strapped to the outside of the woman's abdomen. The device records the movement caused by the uterine muscle relaxing and contracting. The women's uterine activity was measured before exercising and for 30 minutes following the exercise.

The researchers found that neither type of exercise increased uterine activity above normal levels during the 30 minutes after the women stopped exercising. The researchers did not measure the contractions while the women actually performed the exercise. However, Dr. Veille said if the exercise did cause the women to be more susceptible to premature labor, the post-exercise readings would probably have shown increased uterine activity. Even more reassuring, noted Dr. Veille, was that none of the infants born to the women was premature.

Women who exercised regularly before pregnancy can safely continue to exercise during pregnancy, say NICHD-supported researchers. NIH Photo 2112

In addition to monitoring uterine activity, the researchers also measured the fetuses' heart rate and the mothers' heart rate and blood pressure before and after exercising. As expected after any type of exercise, the mothers' heart rate increased. The fetuses' heart rate also increased following exercise, but returned to normal within 30 minutes.

Dr. Veille recommends that women continue to exercise as long as they feel comfortable, but within limits. "If a woman is healthy and exercised regularly before pregnancy, then exercise probably has more benefits than risks," he said. "But if a woman has never exercised before, then she shouldn't start exercising when she's pregnant," added Dr. Veille. Besides giving a woman a positive self-image and sense of well-being, he said, exercise during pregnancy can maintain a woman's muscle tone, strength and endurance. ■

New Technique Being Developed for Rapidly Identifying Microorganisms

Doris Brody

When a patient arrives at a hospital suffering from a severe infection, physicians should initiate treatment immediately. Often they must do this without knowing—for at least a day or, in many cases, much longer—exactly what is causing the infection. The choice of treatment is based on the patient's symptoms and history, and on the physician's experience. Since various disease-causing fungi, bacteria, and viruses respond differently to different modes of treatment, it is important that the physician choose well.

In some cases the clinical microbiology laboratory—that part of the hospital responsible for the isolation and identific tion of microorganisms—can, on the b sis of microscopic examination of a specimen of the patient's blood or ot body fluids or by how such a sample acts to certain chemical staining tech niques, make a relatively speedy rep In addition, many infectious organism can be cultured, or grown, from the spe imen in less than a day and can then b identified using one of the many differe assay systems that are available.

These systems may take a few hours to pinpoint the cause of an infection, providing there are a large number of organisms in the specimen. However, there are many organisms, such as those that cause meningitis, gonorrhea, and Legionnaire's disease, that are difficult to grow or grow very slowly. Identification of some infectious agents can take weeks.

Clearly, any system of identification which would cut the total time required for a confirmed diagnosis could save both lives and money. At Los Alamos Na tional Laboratory in Los Alamos, New Mexico, National Institute of General Medical Sciences grantee Gary Salzman, Ph.D. and co-investigator Charles Gregg, Ph.D. are working on such a system, which could identify microorganisms in minutes without first requiring that they be isolated and cultured.

At present, those assay systems most widely used to identify microorganisms depend on "tagged" or labeled substances that bind specifically (form a chemical union) with a particular infectious organism or to an antibody, produced by the host, to that organism. An antibody is tailored to the infectious or ganism or antigen the way a key is ma to fit a lock.

The binding step is the essential event needed to identify the microorganism. After the antibody binds to the antigenic portion of the organism, the unbound matter is washed out of the specimen and the assay is performed.

The specific tag used may be a radioactive chemical, a fluorescent dye or an enzyme. The organism with its tagged antibody can be detected with an assay designed to specifically measure radioactivity, fluorescence or enzyme activity. Although these so-called immunoassays for rapid identification of the cause of an infection have been greatly improved recently, it still takes several hours to complete them.

Dr. Salzman's system, which grew out of his basic studies of the scattering of light from cells, involves principles quite different from any previously used in clinical microbiology. He employes a technique known as MLS (multiparameter light scattering) to analyze how specimens interact with polarized light. Light from a laser passes through a polarizer and then through a modulator. This bends the polarized light to the right and left in a circular fashion. When a biological sample is placed in the device, the pattern of light scattered by the sample is measured by a spectrometer (an optical instrument for measuring light). The device can use different signal frequencies, each of which brings additional information to aid in identification of the organisms in the sample.

Dr. Salzman believes his system works by recognizing the "packaging" of the genetic material that is unique for each microorganism. Since the genetic material of biological specimens like bacteria, fungi, or viruses is asymmetric, it interacts differently with polarized light coming from different directions. By making many observations and using a computer to tally the results, Dr. Salzman's system has been able to distinguish among very closely related organisms like the viruses from various forms of influenza, dengue fever (a tropical disease), and encephalitis.

Dr. Salzman's present device is a stationary instrument in which the viruses and bacteria in the specimen are identified in a test tube. He is now planning to combine the MLS device with a flow cytometer—a machine that sorts cells extremely rapidly—in order to determine in a matter of minutes, both the identification and an estimate of the relative quantities of microorganisms in samples which contain many different types of organisms, as do most clinical specimens.

The shortened time it will take to make a diagnosis with this system should prove valuable in the treatment of many diseases, including spinal meningitis, septicemia, pneumonic plague, and Legionnaire's disease, illnesses for which prompt diagnosis is particularly important for effective therapy. In some situations it could prevent unnecessary invasive intervention, such as the performance of a Cesarean section in a pregnant woman who has lesions resembling herpes and who is about to deliver a child.

In addition to possibly reducing the incidence of death or permanent damage due to infection, such rapid diagnosis may shorten the time spent in the hospital, and help hospitals better control the spread of infection. Practical development of the device for clinical use will be supported by Mesa Diagnostics, a private firm which hopes to have this system ready for marketing by 1987. ■

Final Results Confirm that Steroid Prevents RDS in Premature Infants

National Heart, Lung and Blood Institute

The National Heart, Lung and Blood Institute (NHLBI), has published the final results of a study in which an adrenal corticosteroid (dexamethasone) was administered to pregnant women to prevent respiratory distress syndrome (RDS) in premature newborns. The study began in 1976 and concluded in 1983. It involved one Canadian and four U.S. clinical centers, which screened more than 8,000 women to enroll the 696 that participated.

After final analysis of the data, the investigators concluded that steroid administration to an expectant mother shortly before she gives birth can prevent RDS in certain premature infants and does not result in any immediately detectable abnormalities among the offspring of the treated mothers.

The Collaborative Study on Antenatal Steroid Therapy was organized following a workshop in which evidence was presented that administering a corticosteroid to an expectant mother at risk for premature delivery shortly before she gave birth hastened lung maturity in the fetus and resulted in more viable offspring. Neonatal (newborn) RDS is a condition in which an infant's lungs have not developed sufficiently and therefore are unable to process enough oxygen for the baby's needs even when pure oxygen is administered.

Infants born prematurely are more likely to have RDS than are infants carried to term, but the underlying cause of RDS is not completely understood. Up to 60 percent of premature infants have RDS, which results in as many as 10,000 deaths per year among liveborn infants. The investigators point out that dexamethasone therapy has the potential to prevent at least 15,000 cases of RDS per year among premature female infants, which is a savings of approximately 200 million dollars in cost of neonatal intensive care.

Women who participated in the study were judged to be at high risk for premature delivery, met other criteria as determined by laboratory studies and agreed to participate in the follow-up testing for their offspring. Participants were randomly assigned to a control group or to an experimental group. The experimental group received up to 20 mg of the steroid dexamethasone administered in four doses 12 hours apart. The control group received placebo injections on the same schedule. The study was double blind, which means that neither the expectant mother nor her doctor knew whether she received the drug or the placebo.

Immediately upon delivery and at specified intervals afterwards the infants received a battery of tests to detect RDS and to answer questions about any short-term and long-term effects on the development of the child.

Early results of the study were somewhat surprising. Dexamethasone was found to lower the incidence of RDS among premature offspring, but these results were confined to female children of single births. Approximately one of every five girls born prematurely to mothers who were not treated with dexamethasone had RDS, whereas only one of every 20 female babies had RDS if their mothers had received the steroid. No effects of the drug were seen in babies born in multiple births or among male offspring. One of every six premature male babies had RDS regardless of whether their mothers received dexamethasone. Another surprising result of the study was the finding that whites in general seem to benefit less (in terms of lowering the incidence of RDS) than do other racial or ethnic groups.

Physiologic, neurologic and developmental tests were scheduled to be performed on the infants at the gestational ages of 40 weeks, 9 months, 18 months and 36 months. During follow-up, 93 infants died, equally distributed between the placebo and steroid group, and another 240 were lost to follow up for other reasons, such as relocation of the family.

Final results of the study indicated that height and weight were slightly greater among the infants of the steroid group at 18 and 36 months. No differences were found between the two groups of infants for head circumference or the presence of neurologic abnormalities. Results of tests measuring psychomotor, developmental and cognitive progress also were similar for the two groups. ■

Surgical Brain Bypass Found Ineffective for Stroke Prevention

Lynn J. Cave

A widely used neurosurgical procedure to direct blood past obstructed brain arteries is no more effective than aspirin and standard hypertension control for preventing stroke, according to an international clinical trial supported by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and reported in the November 7 *New England Journal of Medicine*.

The study concludes that the procedure—known as the extracranial/intracranial (EC/IC) bypass operation—should be abandoned for safer, equally effective medical alternatives.

The EC/IC bypass has been the most common neurosurgical procedure used to prevent stroke caused by a narrowing of the arteries. Several thousand EC/IC bypasses are believed to be performed in the United States each year at an estimated cost of $15,000 per operation.

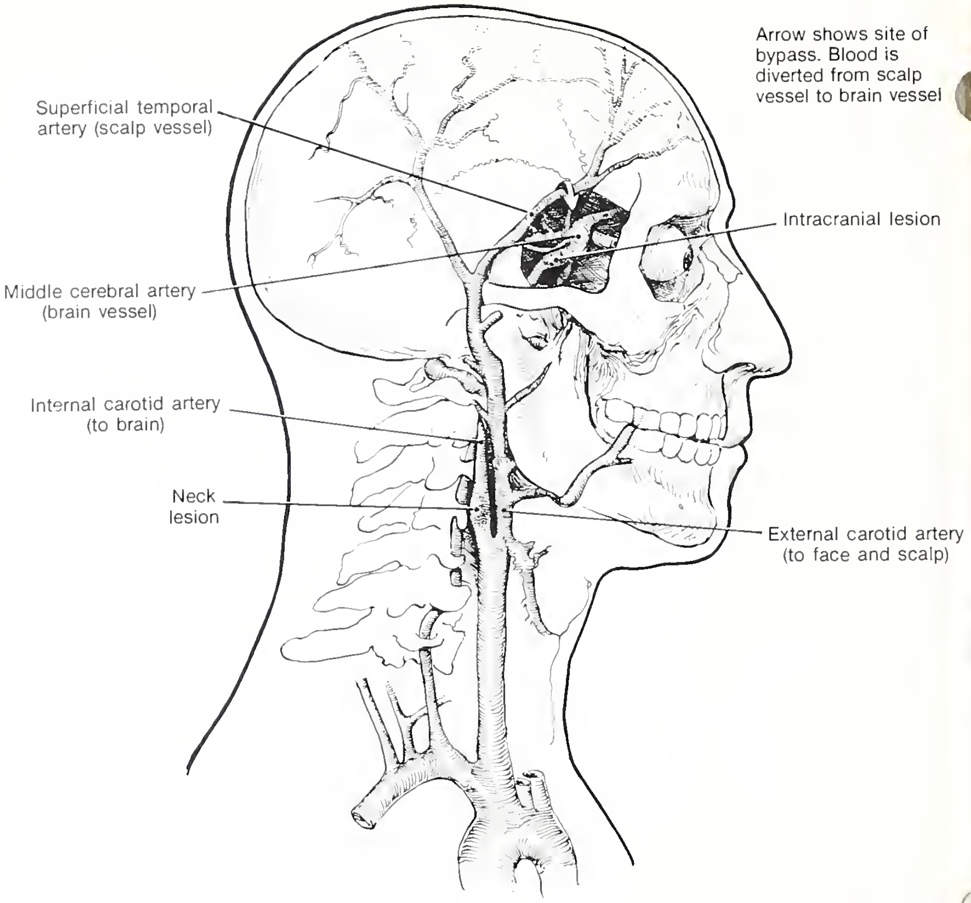
The 8-year NINCDS-supported study, carried out by Drs. Henry J. M. Barnett and Sydney J. Peerless of the University of Western Ontario and their colleagues from 71 centers around the world, showed no significant difference in the number of strokes and stroke deaths occurring between patients who received the EC/IC operation and those who received only medical treatment.

Stroke is the Nation's third leading cause of death and a major cause of long-term disability. Often, stroke is caused by a gradual narrowing of major neck and head arteries as fatty substances build up in them, decreasing and eventually halting the flow of life-giving oxygen and nutrients to the brain.

The EC/IC bypass operation was developed in 1967 to route blood past obstructions in the internal carotid artery or its major branch, the middle cerebral artery. During the operation, a scalp artery located near the temple is passed through a hole in the skull. At a point downstream from the obstruction, the scalp artery is joined to the middle cerebral artery, completing the bypass and replenishing blood flow to the brain.

"The operation has been commonly applied," says Dr. Michael D. Walker, Director of the NINCDS Stroke and Trauma Program. "It intuitively makes sense. But we had to ask, 'Does the surgery make any difference in stroke prevention?'"

The NINCDS began the international controlled clinical trial in 1977 to answer just that question. Over the next 8 years, 1,377 stroke-prone patients participated in this first major randomized test of a neurosurgical procedure.


Arrow shows site of bypass. Blood is diverted from scalp vessel to brain vessel
Superficial temporal artery (scalp vessel)
Intracranial lesion
Middle cerebral artery (brain vessel)
Internal carotid artery (to brain)
Neck lesion
External carotid artery (to face and scalp)

The white arrow shows the site of the bypass. Blood is diverted from scalp vessel to the brain vessel.
NIH Photo 2113

Patients were considered stroke prone if they had suffered a minor, nondisabling stroke or a transient ischemic attack (TIA) within 3 months of entering the study. A TIA is a "little stroke" that temporarily causes symptoms such as numbness, loss of muscle strength, speech difficulty, or blindness. Stroke-prone patients were admitted to the study only if special X-rays showed blockage in specific areas of the internal carotid artery or middle cerebral artery.

All patients received medical treatment: four aspirin a day and aggressive control of high blood pressure. About half also received bypass surgery. All patients were monitored for nearly 5 years through followup visits every 3 months.

"The results of the study are clear cut," says NINCDS Director Dr. Murray Goldstein. "The operation is unnecessary."

The trial showed that strokes occurred slightly more frequently and earlier in patients who had undergone the operation. Although the difference between treatment groups was not significant according to statistical tests, the risks inherent in performing a surgical procedure make medical management the preferred treatment for stroke-prone patients, Dr. Goldstein says.

Other study findings also support this conclusion, he says. The trial showed that when stroke did occur, bypass patients had no better or faster neurological improvement than did patients receiving only medical treatment. Both groups showed a similar drop in the frequency of TIAs, indicating that the bypass procedure was no more effective than medical management for halting these attacks. In addition, the occurrence of stroke-related deaths was the same in both groups.

"We were disappointed that the surgery didn't work better," says Dr. Barnett. He believes clots from elsewhere in the body may have traveled to the brain and caused strokes by choking off blood vessels.

"We do not recommend that patients have this surgery to prevent stroke," Dr. Barnett says.

"I know some neurosurgeons will question the interpretation of the bypass study data," says Dr. Goldstein. "But the data are unassailable."

In addition, he says, this study has "demonstrated to the entire surgical community that controlled clinical trials of a surgical procedure are ethical and feasible. This study has set an example for the rest of surgery to follow."

Only surgeons with a proven success rate for the operation who agreed to perform the procedure according to protocol participated in the study. The performance of surgeons in the study compared well with that of bypass specialists: the frequency of death in the 30-day postoperative period was lower for study patients than that reported in the literature for other EC/IC bypass recipients. The results were the same whether the operation was performed by surgeons in North America, Europe, or Asia.

Another exemplary feature of the trial is that the scientists did not lose track of a single patient. "Unless you make a religion of it like we did, 10 to 15 percent of your patient population can get lost," Dr. Barnett says. One patient in this study was traced to a prison in Holland.

"Controlled clinical trials like this one are extraordinarily efficient for providing answers about the worth of a procedure," Dr. Walker says. "It would have taken many more years of anecdotal and sequential reports to reach a conclusion about the effectiveness of this operation."

In addition to bringing in a relatively quick verdict, the trial has resulted in a large data base of information on stroke patients.

"I expect perhaps 25 to 30 papers to be spun off from this study as the investigators mine the data base looking for cross correlations," Dr. Walker says. "Some of this work may lead to additional important research projects."

But perhaps the most striking aspect of the study is its potential for lowering health care costs. "We calculated that had the 700 patients in our medically treated group undergone surgery in the United States, the cost to the health care system would have exceeded what the NINCDS spent to evaluate the procedure," Dr. Barnett says. Scientists involved in the study speculate that because the EC/IC bypass was found ineffective, insurance companies will evaluate the results and stop paying for the procedure.

The EC/IC bypass operation won't disappear overnight, but the number of operations performed is expected to drop rapidly in the next year or two as more stroke-prone patients receive the safer, equally effective medical alternative. ■

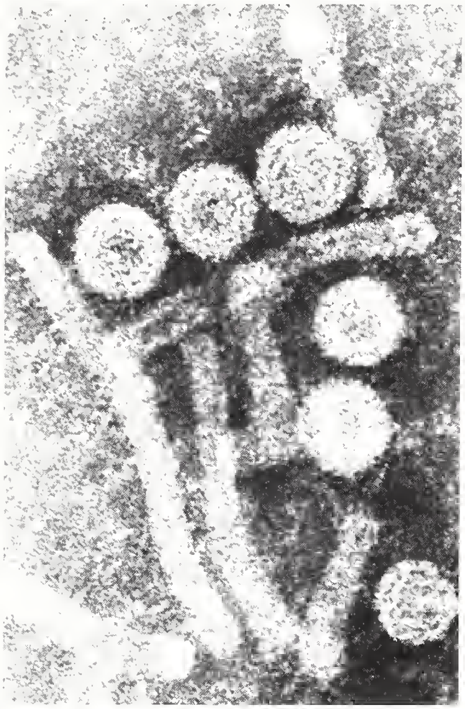
Experimental RDNA Hepatitis Vaccine Found to be Safe and More Effective

Patricia Randall

A new experimental hepatitis B vaccine, produced by genetically engineered mammalian cells, is as safe as the currently licensed vaccine and even more effective in stimulating the immune system, according to a study supported by the National Institute of Allergy and Infectious Diseases (NIAID). The results were reported October 1 at the twenty-fifth Interscience Conference on Antimicrobial Agents and Chemotherapy in Minneapolis by Dr. John M. Zahradnik of Baylor University, Houston.

In the United States, about 200,000 new cases of hepatitis B, a debilitating viral disease of the liver, occur each year. An estimated 800,000 persons are chronically infected carriers. The disease is transmitted by contact with infected blood and other body fluids. Persons at high risk of infection include homosexual men, health care workers, kidney dialysis patients, intravenous drug abusers, and hemophiliacs.

The new vaccine, prepared by Genentech, Inc. of San Francisco, is made by inserting specific genes from the hepatitis B virus into mammalian cells using recombinant DNA techniques. These genes code for hepatitis B surface antigen (the protein that stimulates the body's protective immune response). The mammalian cells are maintained in a continuous culture in the laboratory and can be used as effective producers of hepatitis B vaccine at relatively low cost.



The Dane particles and filamentous form of hepatitis B antigen are shown in this photo micrograph (x150,000). NIH Photo 2114

Cost is a particularly important issue since large quantities of hepatitis B vaccine are needed for areas of the world where hepatitis B is endemic, and entire populations may need to be vaccinated. More than 200 million persons worldwide are chronic carriers of hepatitis B virus, and infection is widespread in many parts of Asia and Africa. The current vaccine is safe and effective, but it is prepared from the blood of hepatitis B carriers and is expensive to produce.

Forty healthy adult men were included in the NIAID-supported study, conducted at Baylor University by Drs. Zahradnik and Robert B. Couch. Twenty were given three doses of the licensed vaccine, and 20 were given three doses of the experimental product. Both vaccines were given at the beginning of the study, one month, and at six month intervals. Other than occasional soreness in the arm at the injection site, no side effects were seen in the vaccinees.

Blood tests, performed by Dr. John H. Gerin at Georgetown University Hospital, showed that ten percent of the vaccinees receiving the experimental vaccine had immune responses within ten days. Within four weeks, 70 percent of these vaccinees had responses. Of those receiving the licensed vaccine, none had a response within ten days and 40 percent had responses within four weeks. At the end of eight weeks, however, 95 percent of both groups showed immune responses. Follow-up will continue for nine months.

This study was supported by the NIAID as part of its program for the accelerated development of new vaccines. Hepatitis B is one of ten diseases or disease categories targeted by the NIAID for prevention by immunization with new or improved vaccines within the next five to ten years. Others include meningitis in infants, gonorrhea, croup and pneumonia in infants and children, whooping cough, influenza, diarrhea, chickenpox, genital herpes, and malaria. ■

Chromosome Walking Provides Scientists with Valuable Tool for Studying Genes

Sandy Hecker

One of the most important recent advances in genetics—the increased understanding of mutations caused by defects in homeotic genes (genes that control the location of developing body parts)—was largely due to a new research technique called chromosome walking. One of the first uses of this technique was to find the precise chromosomal location of a group of fruit fly *(Drosophila melanogaster)* genes known as the bithorax complex (BX-C). Mutations in BX-C cause developmental changes yielding, for example, flies with two pairs of wings instead of the normal single pair.

In 1978 a group of scientists working in the laboratory of the National Institute of General Medical Sciences (NIGMS) grantee Dr. David S. Hogness at Stanford University decided they wanted to isolate and study DNA from several specific areas of the fruit fly genetic material, including that of the BX-C genes. They knew the approximate position of these genes on chromosome 3, but not their precise position. The scientists wanted to

A chromosome is a condensed structure found in the cell nucleus and containing the genes. Chromosomes are composed of DNA and proteins and they can be seen with the light microscope during certain stages of cell division, when they appear as rod-like structures.
NIH Photo 2115

isolate the BX-C genes in order to determine their structure and deduce information about their gene products, which could then help them unravel much of the mystery of the role these genes play in the development of body parts. To isolate the BX-C genes and the two others in which they were interested, Drs. Hogness, Welcome Bender, and Perre Spierer needed a method other than those that existed for isolating genes.

Existing methods depended on a knowledge of the gene's products but the products of the BX-C genes were not known at that time. The researchers began to examine the DNA itself to obtain information about the genes such as the base sequences that compose them, and their precise location on the chromosome. (DNA consists of four subunits called bases that are attached to each other and to the DNA's "backbone" in a particular order. Just as the order of letters in a word gives that word meaning, it is the order of the bases that provides specific genetic information.) At present, it is not possible to determine the exact base sequence of extremely long molecules of DNA, such as the fruit fly DNA molecule that contains all of the genes in an intact chromosome. Thus, the long chromosomal DNA molecule must be broken into small, manageable fragments.

Drs. Hogness, Bender, and Spierer began by obtaining fruit fly gene libraries, a collection of DNA fragments that together represent the organism's total DNA. The NIGMS grantees then developed a method called "chromosome walking" to determine how the chromosome 3 fragments fit together in an intact chromosome. They then applied this information to identify those fragments that contained the genes in which they were interested.

In order to reconstruct the sequence of bases in the intact chromosome from a library of fragments, the scientists needed a starting point. One way to start was to employ a probe—a piece of DNA whose precise location on chromosome 3 they knew. Since a probe will identify the fragments of DNA that contain the base sequence that matches itself, Drs. Hogness, Bender, and Spierer used it to locate the chromosome 3 fragments containing those sequences.

Because the fragments are longer than the probe, some fragments overlapped with the probe in one direction, while others overlapped in the other, effectively extending the known section of the chromosomal DNA. A new probe was then made from the DNA at one end of the extended region (the direction the scientists wanted to "walk.") The process of collecting fragments containing the base sequence present in the new probe was repeated, thereby further extending the "known" section of chromosomal DNA. The original order of the fragments in the intact chromosome was determined by systematically repeating this process. Creating this progressively longer sequence of "known" DNA is how researchers "walk" toward the region in the chromosomal DNA that contains the genes in which they are interested.

This is a karyotype of a normal human female. To make a karyotype, skilled laboratory workers view the chromosomes from one cell of an individual under a microscope, photograph them, and then cut them out of the photograph and arrange them by size in a conventional order called a karyotype. Karyotypes can be made from fetal cells derived from amniocentesis in order to determine chromosomal aberrations that could indicate genetic disease. (Source: NIGMS Human Genetic Mutant Cell Repository, Camden, NJ.)
NIH Photo 2116

Chromosome walking is a very slow process; it takes a month to walk a distance of 50,000 bases along the chromosomal DNA, yet the distance that must be walked between the starting point (initial probe) and the area of interest is often very much longer than this. For example, the bithorax complex was estimated to be about 4 million bases away from the researchers' starting point.

Drs. Hogness, Bender, and Spierer began working toward a gene called *Ace* (which specifies the enzyme Acetylcholinesterase) that they knew is physically closer on the chromosome to the starting point than is the bithorax complex. They very quickly reached it, and encouraged by this success, they continued down the chromosome toward another gene area called *"rosy."* During this work they discovered a chromosomal abnormality called an inversion that enabled them to "jump" to the bithorax complex.

An inversion is an area of a chromosome in which a section of DNA has been broken and turned around, end for end. Geneticists can recognize these inversions and use them to shorten the walking process and move ("jump") from one end of the inversion to the other in a single step. This faster form of chromosome walking is called chromosome "jumping" and helps scientists cover distances on the chromosome more quickly. By this means, the scientists were able to isolate DNA from the bithorax complex in a much shorter time than the six years it would have taken them if they had walked the same distance. After they jumped into the bithorax complex, they walked from one end of this complex to the other. They found that it is over 300,000 bases long and contains many homeotic genes that they identified.

Chromosome walking and related techniques have given researchers invaluable information about the DNA of certain groups of genes. For example, isolation of the individual genes that compose the bithorax complex enabled scientists to use DNA from these regions as probes to look for similar sequences on other chromosomes. This resulted in the discovery of the "homeo box." In genetics, "box" refers to the shortness of a sequence and its similarily among species in which it is found.

Rather than being limited to more traditional genetic studies, which start with a defective protein and then work back to identify the gene responsible for that protein, scientists can now look at the DNA itself and often determine the areas that are blueprints for proteins, and in some cases what type of protein a gene specifies.

Chromosome walking promises to have many more applications in genetics, and is already being used to look for particular genes of interest to researchers, including many that affect humans, such as those causing Huntington's disease and Duchenne muscular dystrophy ■

MEDICAL CAPSULES

Sandra D. Levine

New Facial Restorative Material Developed

A new, more life-like restorative material has been developed to rebuild the face following disfigurements caused by tumors, birth defects, infections and other diseases, and accidents.

Under a grant from the National Institute of Dental Research (NIDR), the comfort, effectiveness and durability of the material—chlorinated polyethylene (CPE)—is being tested on patients by Dr. Lawrence Gettleman and colleagues at Gulf South Research Institute in New Orleans.

CPE has improved molding and elastic properties that prevent it from fraying or tearing at the edges, a problem inherent in currently-used materials such as silicone rubber that requires periodic replacement. CPE can be molded repeatedly, and by imbedding cosmetic pigments, color and texture can be adjusted to duplicate natural complexion. Also, patients can alter the surface coloring of CPE to reflect seasonal changes in skin tones, enhancing its life-like appearance.

SIDS Not Linked to DTP Shots

Contrary to earlier anecdotal reports, a link has not been found between diphtheria, tetanus and pertussis (DTP) inoculations and sudden infant death syndrome (SIDS), which claims 5,000 to 6,000 lives each year in the U.S.

Epidemiologists at the National Institute of Child Health and Human Development (NICHD), in an in-depth nationwide analysis of 716 cases of SIDS occurring during a 15-month period, showed that only 40 percent had received the DTP vaccine. In a control group matched by age, race and birth weight, 55 percent of babies without SIDS had been immunized.

Pathological examinations were made of 26 different tissue samples from each SIDS case between two weeks and two years of age and not hospitalized at the time of death. Detailed interviews were conducted with the mothers of both groups regarding their babies' health and immunization histories.

The final report on the epidemiology of SIDS to establish a profile of infants at risk will be published in 1986. A preliminary report is available from NICHD, Office of Research Reporting, Bldg., 31, Rm. 2A32, Bethesda, MD 20892.

Conference Held on Swallowing Disorders

A multidisciplinary conference on swallowing and swallowing disorders was held recently at the NIH. Co-sponsored by the American Speech-Language-Hearing Association, it was the first conference to bring together medical professionals conducting basic or clinical research on normal and abnormal swallowing.

Swallowing problems encompass a broad range of conditions, ages, and medical disciplines. Conference participants emphasized the need to develop a team approach to diagnosis and treatment, including speech pathologists, radiologists, oral surgeons, dieticians, gastroenterologists, otolaryngologists and neurologists.

Drs. Barbara Sonies, Thomas Shawker and Maureen Stone at the NIH Clinical Center presented an update on their research on ultrasound techniques to study the oral phase of swallowing, including tongue dysfunction. Since ultrasound imaging eliminates many of the limitations of X-ray fluoroscopy such as radiation hazard and inability to delineate much soft tissue, it is expected to prove valuable as a routine clinical technique to investigate swallowing and speech disorders.

Proceedings of the conference will be available in early 1986.

U.S. and U.S.S.R. Cooperate on Juvenile Arthritis Study

The first cooperative study by the U.S. and the U.S.S.R. on the treatment of juvenile arthritis has been completed. The controlled trial of 162 children between the ages of 18 months and 17 years, who were followed for more than one year, evaluated the safety and effectiveness of d-penicillamine and hydroxychloroquine, drugs that are beneficial in adults with rheumatoid arthritis. The U.S. portion of the study was funded by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK).

In 13 U.S. pediatric rheumatology centers and five centers in the U.S.S.R., the children were divided into three groups—one given d-penicillamine; another given hydroxychloroquine; and a control group that received placebos. Throughout the trial, all patients continued to receive a nonsteroidal anti-inflammatory drug.

According to Dr. Earl Brewer, an NIADDK-grantee at Texas Children's Hospital in Houston, although more than half of the children in the two drug groups showed improvement, a similar number in the group receiving placebos also improved. Therefore, short-term therapy with these drugs did not provide the children with a significant advantage over treatment with the nonsteroidal anti-inflammatory agent alone.

New Methods Developed to Study Bone Conditions

Two new, more effective procedures to study bone conditions that lead to fractures are being developed with support from the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases (NIADDK).

At Thomas Jefferson University in Philadelphia, Dr. Peter Frasca and colleagues have designed a method to evaluate the failure mechanism in osteogenesis imperfecta (OI) bone and to differentiate it from normal bone. OI is a genetic disease characterized by fragile, poorly calcified bones that fracture easily.

Using micro-mechanical testing that applied a bending stress to OI and normal bone fragments, they found that in OI there is malformation of the collagen fibers. With this ability to evaluate OI bone, physicians will be able to assess how best to reinforce and strengthen it.

At the Mayo Clinic, a new biplanar X-ray method to study the vertebral fractures of spinal osteoporosis has been developed by Dr. E.Y. Chao and colleagues. These fractures are difficult to measure and monitor consistently by standard X-ray.

The new technique determines incidence and progression of fractures by measuring geometric shape changes in the vertebrae of osteoporotic patients. Seven age-matched normal controls and four postmenopausal osteoporotic patients were studied to determine its accuracy and reproducibility. Also, 68 patients being treated with fluoride and calcium were analyzed. Patients were positioned in a special metal frame with shoulders and pelvis immobilized, and the frequency, type and location of intervertebral fractures were analyzed. Patient positions were recorded so that identical postures could be reproduced at subsequent evaluations—a unique advantage of this technique, which is considered reliable in patients with moderate disease and no severe spinal deformity.

Editors of publications may request a glossy print of the numbered photographs appearing in this issue.

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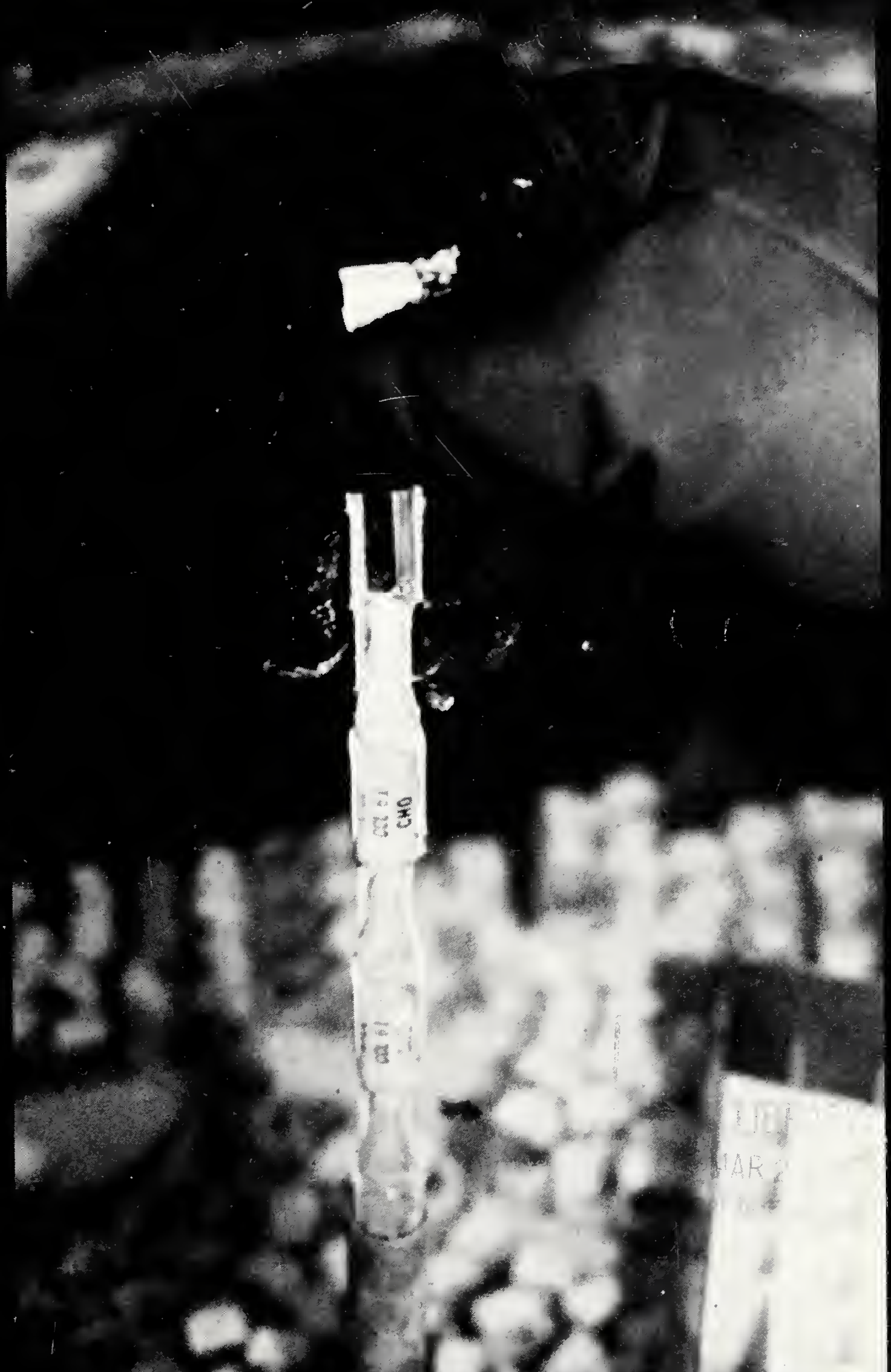

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NEWS & FEATURES from NIH

Vol. 86. No. 2

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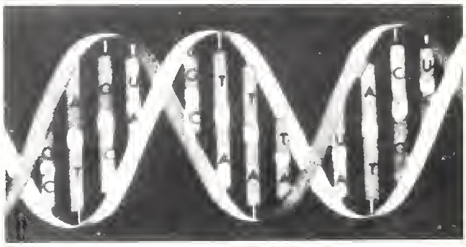
Because of research conducted over the past few years, the management of kidney stones has undergone a revolution. Scientists supported by the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDK) recently attended a conference to contribute their knowledge and to discuss the latest research advances. One of the most dramatic developments to date is the use of extracorporeal shockwave lithotripsy (ESWL), a technique that literally crushes kidney stones using shock waves. ESWL may eventually replace most surgery to remove stones. However, the scientists explained that drug and diet therapy is still useful in some cases to prevent and treat kidney stones. See page 2.

NIH scientists are interested in studying the fascinating relationship that exists between the retina and the brain's pineal gland—a so-called primitive organ whose function, until recently, has remained a mystery. In lower animals, the pineal gland acts as a basic light-sensing organ, but not so in mammals, where its function is less well understood. The appearance of similar proteins or enzymes in a variety of species seems to link the two organs and suggests common evolutionary development. This and other findings have renewed interest in the pineal gland and has led researchers to believe that this organ may have a more sophisticated role than previously thought. See page 4.

NIH PHOTO 2117

NIH-supported scientists have recently reported that a promising new antiviral drug—acyclovir—is more effective than the currently used treatment, vidarabine, for herpes encephalitis. This serious brain inflammation causes a life-threatening neurologic illness that often leaves its survivors severely debilitated. In the current study, the researchers compared the two antivirals and found that more patients survived with acyclovir than with vidarabine and among the survivors there were fewer impairments. These results offer new hope to the victims of this devastating viral disease. See page 6.



NIH PHOTO 2118

From time to time, *News and Features from NIH* will include a section on biotechnology to present NIH scientific developments related to this growing field of research. Biotechnology is broadly defined as research involving living organisms (or parts of living organisms) to make or modify products. More specifically, this includes recombinant DNA research, research involving monoclonal antibodies and bioprocess technology. Basic biomedical research contributes to biotechnology by leading to discoveries that may have commercial application and by providing the tools needed by scientists to carry on this important effort. In this issue we are highlighting advances made possible from one particular aspect of biotechnology, research using recombinant DNA techniques, such as gene identification, cloning and the use of genetic probes; all more commonly known as genetic engineering. See page 10.

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Research Advances Cause a Revolution in the Management of Kidney Stones

Jim Fordham

Research on the causes and treatment of kidney stones has been so successful over the past few years that management of the disease has now entered a new era. This revolution in medical and surgical care was described by scientists supported by the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDK) at the annual meeting of the American Society of Nephrology, held recently in New Orleans.

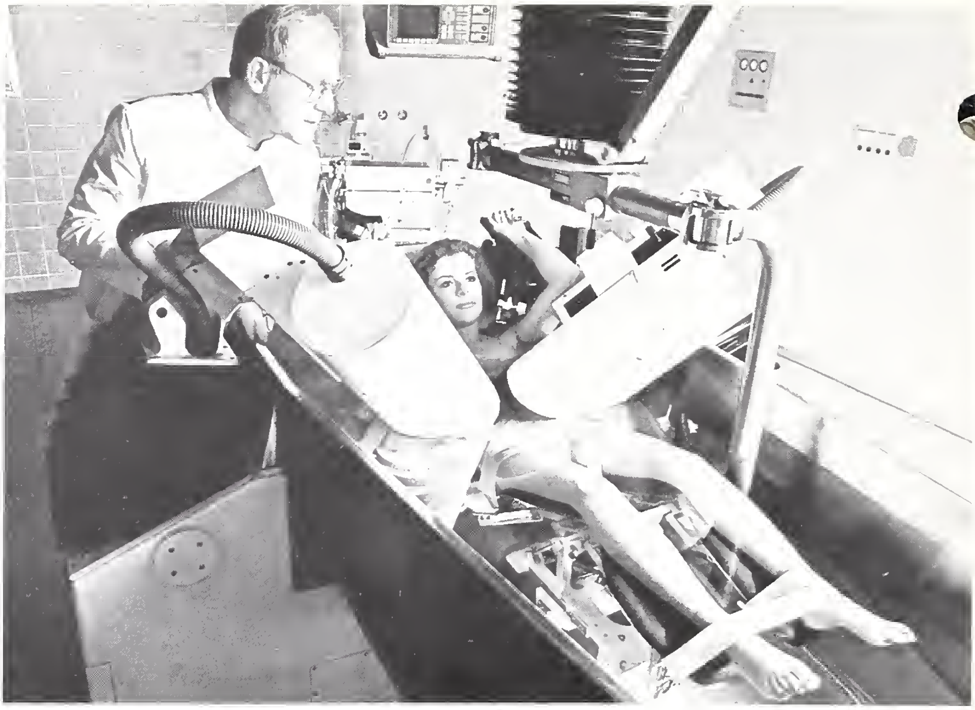
The most dramatic and expensive innovation is the stone disintegrating technique known as extracorporeal shockwave lithotripsy (ESWL), or simply "shock wave therapy." The procedure was developed in Germany and promises to replace most surgery for all types of kidney stones. In the United States, there are approximately 500,000 new cases of kidney stones each year, by some estimates.

The $2 million device that provides this modern miracle is called the lithotripter, or stone-crusher. The instrument delivers high energy shock waves from an underwater high-voltage spark to disintegrate stones while the patient reclines in a water bath.

The kidney stone, targeted by X-rays, receives between 1000 to 2000 blasts, focused by ellipsoidal reflectors. Each blast lasts less than 1 microsecond, penetrates the kidney stone and shatters it as the waves bounce back from the surrounding soft tissue of the body and collide with oncoming waves. The tissue around the stone remains essentially undamaged as the pulverized fragments are subsequently passed in the patient's urine.

The advent and use of the lithotripter was discussed by NIADDK-supported scientist Dr. Birdwell Finlayson of the College of Medicine of the University of Florida, Gainesville, one of the first scientists in the U.S. to employ the stone-crusher experimentally. (The device was approved by the Food and Drug Administration in 1984 and is now being used in approximately 55 medical centers around the U.S.)

Dr. Finlayson described the development of the device in Germany by Dornier System GmbH, an aviation company that learned about shock waves while dealing with the window-shattering booms from supersonic aircraft. In 1974, Dornier engineers were approached with the idea of applying their knowledge of shock waves to the pulverization of kidney stones. They accepted the challenge and subsequently developed ESWL in collaboration with Dr. Christian Chaussy and his colleagues at the Department of Urology and the Institute for Surgical Research at the University of Munich, West Germany.



The patient lies in a reclining chair that is lowered into a tank of water, which contains an electrode to create shock waves that will cause the kidney stone to break up. Doctors can watch the stone as X-rays are taken (machines are on either side of the patient). NIH PHOTO 2119

"ESWL is an extremely powerful technique," said Dr. Finlayson. "We can use it to treat stones anywhere in the urinary tract." He said the procedure can be used to remove stones in nearly all patients. The only contraindications, he said, are pregnancy, renal artery aneurysm (blood-filled dilation of a blood vessel), presence of a pacemaker, problems with anesthesia, or anatomic obstruction below the stone.

On another side of the revolution, scientists have been developing drugs to prevent recurrent formation of kidney stones. Dr. Jacob Lemann, who receives support from the NIADDK at the Medical College of Wisconsin, described the composition of kidney stones, discussed their relative frequency among patients, and reviewed current therapy and prevention of stone disease.

Dr. Lemann reiterated the advice commonly given to patients at clinics specializing in the treatment of stones: Drink more water; restrict dietary calcium and protein; avoid oxalate-rich foods, such as broccoli, cabbage, brussel sprouts, grapes, coffee, tea, cocoa and other foods and beverages.

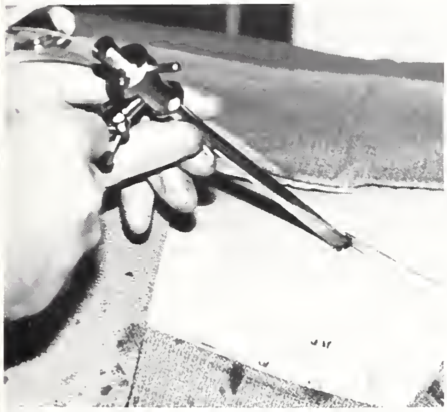
Dr. Lemann recommended these measures for most patients who had formed a stone, but minimized the value of other advice sometimes offered in stone clinics, such as to restrict vitamin C or foods containing sugar.

"Vitamin C is widely used, but patients with stones related to the use of large doses of vitamin C are rare," he said. "Similarly, patients who eat large quantities of sweets or oxalate-rich foods are unusual." Dr. Lemann said such patients should receive appropriate advice when they are identified, but that these restrictions often are not necessary for other stone-formers.

The candidates for preventive drug therapies, said Dr. Lemann, are those patients who have experienced a complicated first stone, residual stones, or recurrent stones.

Thiazides are the drugs used most widely to prevent calcium stone formation. They are clearly effective in reducing urinary calcium excretion, said Dr. Lemann, but they may produce side effects, including diabetes, potassium depletion, and impotence. He cited studies by American and Swedish investigators showing that a large proportion of patients treated with thiazides remain stone-free.

Dr. Lemann also explained that inorganic phosphate supplements are effective in reducing intestinal calcium absorption, augmenting excretion of salts, and reducing crystal formation. He cited a study by Dr. Lynwood H. Smith, Jr., and his associates at the Mayo Medical School, Rochester, Minnesota, showing phosphorus supplements to be more than 90 percent effective in preventing new stone formation. He said that diarrhea is a major side effect of phosphate therapy, particularly when treatment is first started.



Stones can be removed by inserting an ultrasonic or electrohydraulic probe through the skin to the area of the stone in the kidney. Energy from the probe disintegrates the stone and the fragments are drawn from the body.

NIH PHOTO 2120

Dr. Lemann discussed studies by U.S. researchers showing that sodium cellulose phosphate (SCP) effectively limits intestinal absorption of dietary calcium in cases of "absorptive hypercalciuria," a stone-forming disorder frequently associated with increased absorption of calcium from food. He said that Swedish investigators, however, have found the response of patients to SCP no better than the response of control patients, who were merely advised to increase their fluid intake and practice dietary restrictions. (SCP preventive therapy for stones was approved by the FDA in 1982.)

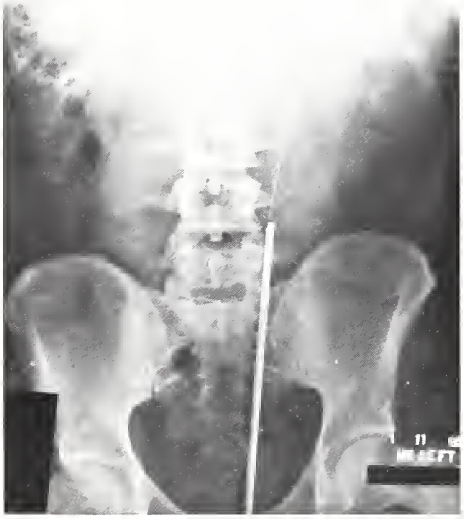
Dr. Lemann also discussed the use of allopurinol, magnesium, and alkali as preventive therapies against recurrent stones. He said allopurinol has been found effective in uncontrolled trials in patients who excrete excessive amounts of uric acid. Magnesium has been found "possibly effective" in treating calcium stone disease in controlled and uncontrolled studies. Alkali, which reduces urinary calcium excretion and increases urinary citrate excretion, has been found effective in uncontrolled studies, but controlled trials have not yet been reported, he said.

Dr. Fredric L. Coe, an NIADDK-supported scientist at the University of Chicago, also discussed prevention of stones, emphasizing that while the lithotripter is a powerful therapy, it does not mean that drug therapy in stone disease is less important.

He presented data to explain the relative proneness of men to stone disease. Men as a group are four times more likely than women to produce stones. The biochemistry of normal women appears to provide some protection against stone formation. Some women who form stones have "supersaturated urine," said Dr. Coe. They excrete high levels of calcium in their urine, which also shows high levels of oxalate, uric acid, and low concentrations of citrate. Female stone-formers also tend to be comparatively large women, he said.

Dr. Coe stressed the importance of measuring levels of urinary citrate in patients who form kidney stones. Citrate is a substance normally found in urine. He suggested that physicians should pay more attention to the problem of low urinary citrate (hypocitraturia).

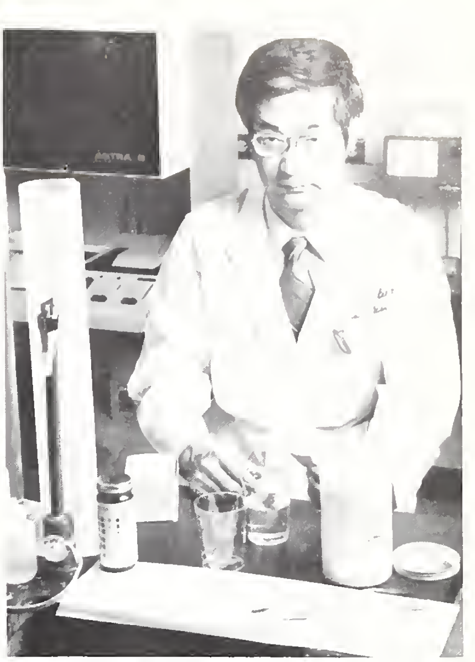
Hypocitraturia affects about 50 percent of all people requiring medical treatment for active stone disease. It is one of the conditions that can now be treated preventively with potassium citrate, an "inhibitor" of stone formation that prevents crystallization of stone-forming calcium salts.



Some stones can be removed by passing a ureteroscope (a flexible viewing instrument) up into the bladder. This X-ray shows the ureteroscope inserted into the left ureter. The stone can be grasped and withdrawn with a basket-like device, shown in this X-ray

NIH PHOTO 2121

Potassium citrate, approved by the FDA last year, was developed by NIADDK grantee Dr. Charles Y.C. Pak of the University of Texas Health Science Center in Dallas. When patients with recurrent stones composed of calcium oxalate or calcium phosphate are treated with potassium citrate, the need for further surgery is virtually eliminated. Since the majority of stones formed by patients are composed of calcium, it is thought that, at present, perhaps hundreds of thousands of patients could benefit from potassium citrate therapy.



NIADDK-supported scientist Dr Charles Y C Pak has developed two drugs, potassium citrate and sodium cellulose phosphate, that have been approved for the prevention of kidney stone formation

NIH PHOTO 2122

Dr. Coe reemphasized the fact that physicians should recognize that measuring citrate levels in urine is just as important as measuring a patient's urinary calcium, and he called for more testing for hypocitraturia ■

This kidney stone operation took place in France in 1682 The lithograph was done by Tolet.

NIH PHOTO 2123

Pineal Gland and Retina Researchers See Eye to Eye

Leslie Fink

Experiments conducted over the past decade by scientists studying the eye's retina and the brain's pineal gland have revealed striking similarities between the two organs. Although scientists a century ago acknowledged some of these similarities, modern scientists—entrenched in vision or brain research—have only recently begun to look again to each other for possible links.

Two separate groups of scientists have studied the pineal gland and the retina, according to David Klein, a pineal researcher at the National Institute of Child Health and Human Development (NICHD). "The people who study the pineal gland in mammals don't study the retina, and, in general, the opposite is true," he says.

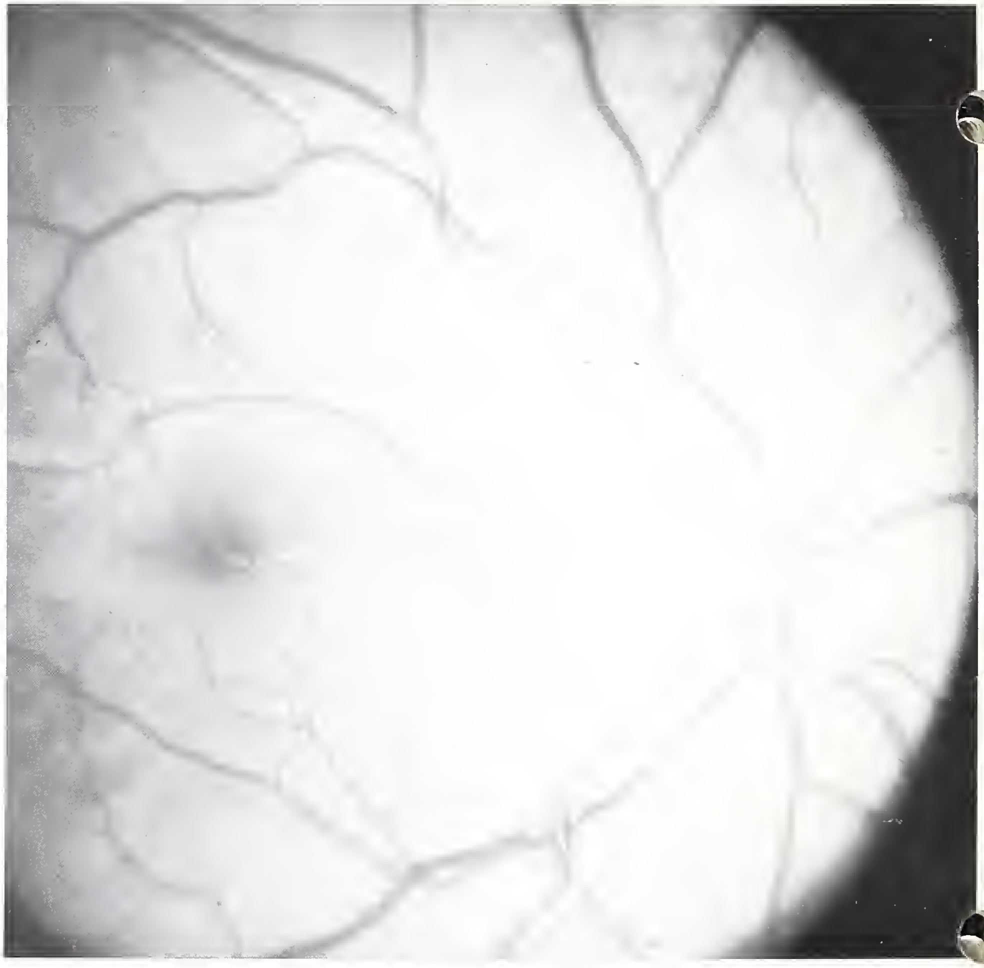
But when researchers from these two different disciplines met to exchange ideas at the first Symposium on Pineal-Retinal Relationships held in Sarasota, Florida, last spring, they returned to their laboratories feeling that they were indeed related.

"It was like finding a relative you didn't know you had," says Paul O'Brien, a scientist at the National Eye Institute (NEI) who, along with Klein, organized the Sarasota meeting. "We are eager to know just how much we have in common."

Biomedical researchers know the pineal gland best as a neuroendocrine organ located in the brain that regulates seasonal changes in physical characteristics, such as coat color, and breeding cycles in some animals. The gland may also affect mood in humans. Controlled by special nerve circuits in the brain, the pineal gland produces melatonin rhythmically—large amounts at night and small amounts during the day.

Chemicals in the retina—the wall of cells located at the back of the eye—convert light into signals that travel along nerve pathways to the pineal gland. There the signals influence the gland's production of melatonin. The hormone then triggers changes in the function of reproductive glands and organs in animals that reproduce only at certain times of the year. As daylight increases from spring to autumn, the different amounts of melatonin produced cause dramatic physical and behavioral changes: bucks grow new antlers or lose their old ones, some rodents change their coat color, and many animals get the urge to migrate or breed.

The role melatonin plays in humans is less established than in animals. Certain studies have linked the hormone to a form of depression called seasonal affective disorder, or SAD, that begins in autumn and lasts through winter. In an experimental therapy, SAD patients in autumn and winter are exposed to bright lights that imitate the amount of light in spring and summer. Although some SAD patients improve with this therapy, researchers are unsure whether the improvement is directly due to changes in the pineal's production of melatonin.



A healthy retina. Not only is this organ important in vision, in animals it also produces chemicals that trigger hormonal responses important in reproduction. This and other findings have stimulated vision researchers to link up with brain researchers in studying how the retina and the brain's pineal gland interact.

NIH PHOTO 2124

Although animal studies have linked the eye and light to the pineal gland, interest in the similarities between the pineal gland and the retina has been slow to develop. In humans, indeed all mammals, the gland itself appears to have no direct light-sensing ability. In fish, birds, and reptiles, though, it acts as a primitive eye, sensing light and dark.

Comparing the anatomy and function of the two organs across species, scientists began to suspect that the pineal and the retina are strongly linked. Proteins once thought to be present in only one of the organs, for example, are being found in the other as well. So-called retina proteins involved in light processing— rhodopsin, transducin, retinol-binding protein, the S-antigen, and rhodopsin kinase—have recently been found in the pineal glands of some cold-blooded animals. The glands of these animals, including fish, reptiles, and amphibians, are directly sensitive to light.

Likewise, melatonin, once thought to be unique to the pineal gland, has also been found in the retina. While the functions of these substances in their "native" tissues have been well studied, scientists know little about what melatonin does in the retina or what rhodopsin kinase does in the pineal gland.

Many of the vision enzymes found in the pineal gland, such as transducin, the S-antigen, and rhodopsin kinase, are, in the eye, part of a process called transduction that converts light into neurochemical signals. These signals travel from the retina along nerve pathways to the brain, providing information about the image. Transduction has preoccupied retina scientists for many years. Their work will be invaluable to researchers in the pineal camp who are studying the possible role of transduction enzymes in the pineal gland.

The enzyme rhodopsin kinase, for example, in the eye adds phosphate molecules to the light-sensitive protein rhodopsin, thus regulating a chain of biochemical events in the vision process. Because rhodopsin kinase has also been found in the pineal gland, Klein and his colleagues are looking in that gland for a molecule with chemical properties similar to light-sensitive rhodopsin.

"Our job as physiological chemists is to figure out what these retina proteins are doing in the pineal gland," says Klein. "If they didn't have a function, they probably wouldn't be there."

Collaborating with Robert Somers of the National Eye Institute, (NEI) Klein and co-worker Tony Ho will mix rhodopsin kinase isolated from the retina with pineal cell membranes. If the pineal cells contain rhodopsin, or a molecule like it, the scientists will find the substance using radioactive "detector" molecules. According to Klein, a rhodopsin-like molecule in the pineal gland could be a membrane receptor that regulates neurochemical events in much the same way that rhodopsin regulates vision signals in the eye.

Transduction enzymes in the pineal gland strongly suggest an evolutionary link between the retina and the pineal gland, says Klein. "It is now my view that the pineal gland—the so-called third eye—was the first eye. The primitive visual organ was a single 'eye' that had only to convert light into chemicals. The retina and bilateral vision developed later on," he said.

Scientists have long noted that the process of development mirrors evolution. During fetal development, both the retina and the pineal gland arise from common embryonic cell layers. Although at birth, pineal cells in mammals appear to have no light-sensing properties, studies have detected such properties in pineal cells from fetal rats.

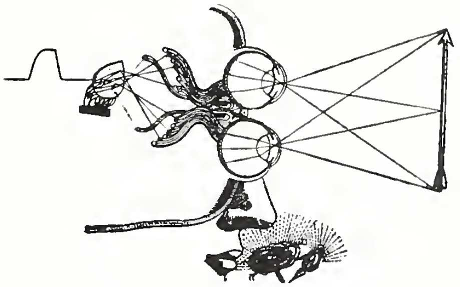
Like the pineal gland, the retina produces melatonin rhythmically. At about the same time the retina stops producing melatonin, elongated cells called rod cells begin a process called disc shedding, in which the end of the cell repeatedly drops off like slices cut from a banana. According to Paul O'Brien, the retina's rhythmic production of melatonin may control cyclic disc shedding.

By exchanging ideas, the two groups of scientists have begun to share tools with which to study the genes that control the production of certain enzymes in the pineal gland and retina. Together the team is isolating from retina cells a portion of the gene that encodes the S-antigen, a protein strongly implicated in the eye inflammation uveitis. In this sometimes blinding condition, the body's immune system, which normally attacks foreign invaders such as bacteria and viruses, turns against its own tissues—in this case the cells of the eye.

Although the S-antigen has been found in the pineal gland too, its function in that organ is not yet known. Using probes made from pieces of DNA, the scientists are looking for similarities in the retina and pineal S-antigen gene. These experiments may tell whether the gene in both tissues is identical, or whether it has changed during evolution. Comparing the arrangement of the amino acid subunits of the S-antigen can also provide clues to when two eyes and bilateral vision developed from a single light-sensing organ.

While the Sarasota meeting focused on rediscovered links between two apparently diverse groups of researchers, the picture that unfolded there may seem obvious in hindsight: tissues related both in the embryo and throughout evolution share a common biochemistry and perhaps common functions. "Only in retrospect does it seem obvious," says Klein. "But," he adds, "you can't establish facts based on what seems obvious. You have to establish facts based on science. Just because something seems obvious doesn't mean it's true." ■

More on the Pineal Gland ...



The relationship between the retina and the brain's pineal gland (graphically depicted above) was recognized by scientists a century ago. The pineal gland has been called the "third eye", which scientists now believe was actually the first eye—existing early on in development—converting light into chemicals. New findings have strengthened the link between the two organs and renewed the interest of modern scientists in the pineal gland.

NIH PHOTO 2125

Turning a popular idea on its head, scientists have discovered that the pineal gland—once thought of as only a hormone-releasing gland located in the brain—is also "hardwired" by nerve circuits to other areas of the brain that may influence mood and behavior. These connections may help explain the pineal gland's role in biological rhythms and behavior, including a form of depression called seasonal affective disorder, or SAD.

"It dramatically changes our concept of the mammalian pineal gland," says David Klein, a neuroscientist at the National Institute of Child Health and Human Development (NICHD), who heads the international research team reporting its findings in a recent issue of *Science*.

"Everyone thought the pineal gland only worked like a radio, sending hormonal messages diffusely through the blood like a radio sends its signals through the air," says Klein. "But it may also work like a telephone, sending messages directly to specific targets through nerves that act like phone wires."

Scientists have known that the pineal gland of cold-blooded animals connect directly to other portions of the brain. Communicating with the brain in this way the pineal gland is thought to help control daily rhythms for sleep and wakefulness.

But, says Klein, it became a "popular idea" that the gland in humans and other mammals had no direct communication with the brain. "The idea reflected growing interest among American scientists in melatonin," a hormone produced by the pineal gland, says Klein. "Today most researchers work within the confines of that idea."

Recently, Klein turned to his colleagues at the Justus-Liebig University of Geissen, in West Germany, to study pineal cells in the hamster brain. Earlier work by scientists studying the eye's retina had shown that cells from both the retina and pineal gland contain a protein called the S-antigen. So, Klein and his coworkers borrowed an antibody the eye researchers developed to help them locate S-antigen-containing cells.

Looking through a special microscope at thin, antibody-coated slices of brain tissue, the scientists saw brightly colored threads running from pineal cells to brain regions known as the posterior commissure and the habenula. These regions in turn connect to brain areas that influence mood, sleep, and behavior.

"This forces us to re-examine past data for the possibility that the pineal gland might be functioning by way of nerves rather than hormones," says Klein. "What did we miss that might be explained by this?"

One possibility, Klein suggests, is how the pineal gland might influence SAD, a form of depression that occurs as days grow shorter in winter and disappears when days grow longer in spring. Because melatonin levels in humans appear to be controlled indirectly by the amount of light, SAD researchers have focused mainly on melatonin as the key to this form of depression. Despite their rigorous efforts to implicate melatonin, though, the researchers have been unable to link melatonin directly to SAD. Some have even abandoned the idea.

But because many SAD patients improve when exposed to bright light, Klein still suspects that the pineal gland plays a role in the disorder. "Maybe the pineal plays a role in mood through these neural connections," he says.

And despite the general antomic similarities among mammals—hamsters and humans—Klein cautions that only continued research will tell whether the nerves he and his colleagues discovered in hamsters exist in humans as well. Still other research must ferret out exactly how the pineal gland affects human biological cycles and behavior. ■

Acyclovir Improves Outlook for Victims of Herpes Encephalitis

Esther McBride/Judy Murphy

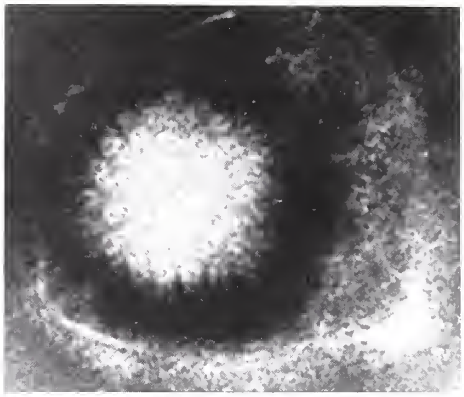
National Institutes of Health (NIH)-supported scientists have recently reported that the antiviral drug acyclovir is clearly more effective than vidarabine, the currently available treatment for herpes encephalitis. The drug greatly improves chances of survival, reduces hospitalization and increases the likelihood of a return to normal function in persons suffering from this serious brain infection. This research was jointly supported by the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), and the Division of Research Resources (DRR).

"This study, which demonstrates that acyclovir is superior to vidarabine, is very important for several reasons," noted Dr. Richard J. Whitley, of the University of Alabama at Birmingham and coordinator of the study. "We now have the ability to greatly increase a person's chances of returning to normal functioning, especially if treatment is begun early after onset of symptoms. The study demonstrates that acyclovir not only improves one's chances of surviving the infection, but also improves the quality of life for many of those who recover."

Herpes encephalitis, which is estimated to afflict several thousand Americans each year, is similar to other types of brain diseases in its symptoms of fever, headache, and delirium and its potentially devastating effects on the central nervous system. It is caused by the herpes simplex virus and can be definitely diagnosed only by brain biopsy.

Prior to the licensing of the antiviral drug vidarabine in 1978, fewer than one-third of herpes encephalitis patients survived, and most survivors suffered severe neurologic dysfunction. Vidarabine nearly doubled survival from this disease, yet mortality remained high and neurologic impairment was common in survivors.

In 1981, the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group undertook a study aimed at comparing the effectiveness of vidarabine with that of a new antiviral drug, acyclovir, in improving the prognosis of patients with herpes encephalitis. In its recently published report on the research in the *New England Journal of Medicine*, the study group presented its findings in 69 patients with biopsy-proven herpes encephalitis. Among the patients receiving acyclovir, 72 percent survived compared with 46 percent of patients receiving vidarabine. The results were even more dramatic in young patients given acyclovir, of whom 95 percent survived.



An electronmicrograph (EM) negative of a complete herpes virus magnified at 275,000. (Photo courtesy of Dr. J. Almeida and Burroughs Welcome Company).

NIH PHOTO 2126

The severe neurologic consequences of herpes encephalitis make the availability of an effective drug critical for those surviving the acute infection. After 6 months, 38 percent of patients receiving acyclovir were functioning normally compared with 14 percent of the patients treated with vidarabine. Nine percent of acyclovir-treated patients had moderate disability compared with 22 percent of the vidarabine-treated patients.

Severely ill patients who were comatose or semi-comatose and who were treated with acyclovir experienced increased survival compared with those treated with vidarabine. However, among the survivors in this category, a higher percentage of those treated with acyclovir suffered severe debility or infirmity. These findings underscore the importance of early diagnosis and treatment of herpes encephalitis.

Acyclovir has been widely used in the experimental treatment of a variety of herpesvirus infections. Oral acyclovir was approved by the Food and Drug Administration in 1985 for use in treating severe primary and recurrent episodes of genital herpes.

Although antibiotics have been available for nearly half a century to combat bacterial infections, physicians have only recently had available agents that are effective against viruses yet nontoxic to the body cells in which the viruses reside.

The NIAID Collaborative Antiviral Study Group, comprised of investigators at more than three dozen research institutions, was established in 1972 to evaluate promising new drugs effective against severe herpesvirus infections. The study group has conducted evaluations of treatments for neonatal herpes, herpes zoster, and mucocutaneous herpes in immunocompromised persons, in addition to herpes encephalitis. Analysis is under way of the effectiveness of vidarabine and acyclovir in treating neonatal herpes. ■

Biological Factors May Cause Predisposition to Borderline Personality Disorder

Rex Cowdry, M.D.

Current research at the National Institute of Mental Health (NIMH) suggests that there may be biological underpinnings to the syndrome called borderline personality disorder. This disorder accounts for 5–15% of all psychiatric hospitalizations.

Individuals with borderline personality disorder have marked mood swings in relation to specific events, particularly episodes of severe dysphoria (mental agitation marked by depression, anxiety and rage) in response to apparent rejection or failure. In addition, they have episodes where they lose control of their behavior, manifested by taking frequent overdoses, cutting wrists, going into rages, or engaging in physical attacks. Ego functions are impaired, such as the ability to think about a situation rather than simply reacting, the ability to anticipate consequences, and the ability to assess people realistically rather than idealizing or devaluing them.

Originally, the mood swings and behavioral loss of control were assumed to occur because of the impaired ego function. The poor ego development was attributed to problems with psychological development often related to early experiences and upbringing. There is now increasing evidence that there are biological factors which predispose to borderline personality disorder, and researchers are entertaining the possibility that the ego problems are at least in part a result of underlying biological problems.

A number of research groups have shown that classical mood disorders (manic-depression and major depression) commonly occur in borderline individuals, in addition to the atypical mood swings which characterize the disorder. The NIMH group has in addition observed the frequent occurrence in borderline patients of symptoms (abrupt and transient mood changes, perceptional distortions, and deja vu) commonly observed during seizures of the limbic system, a deep area of the brain closely connected with the regulation of mood and aggression. These observations led the researchers to speculate that low thresholds for activation of limbic structures may be involved in the development of borderline personality disorder.

Procaine, a local anesthetic which activates limbic areas of the brain, was administered to 15 patients with borderline personality disorder and a similar number of normal individuals. It produced dysphoric states in two-thirds of the borderline patients and none of the normal individuals. The dysphoria appears to be associated with the appearance of high frequency EEG activity over the temporal lobe of the brain, a limbic structure.

The group also conducted a drug treatment study with 16 patients. Participants in the study received a randomized sequence of a placebo and four medications (a monoamine oxidase inhibitor antidepressant, an anticonvulsant, an antianxiety agent, and an antipsychotic agent), each administered for a 6-week period. "Blind" raters observed significant improvement with two medications when compared with placebo: the MAO inhibitor and the anti-convulsant. The response patterns, however, were different with these two medications.

The monoamine oxidase inhibitor (antidepressant) produced overall improvement in a number of measures of mood (depression, anxiety, anger, and sensitivity to rejection) and in impulsivity and suicidality. The anticonvulsant produced significant improvement in these measures also, but the positive effects on mood were less pronounced and the improvement in behavioral control was more striking.

The benefits with antidepressant treatment support the hypothesis that borderline personality disorder is related to more typical mood disorders, while the noteworthy decreases in impulsive and self-injurious behavior produced by the anticonvulsant support the hypothesis that low thresholds for excitation in brain structures contribute to the behavioral problems. In future research, NIMH scientists are planning PET (positron emission tomography) scan studies in patients with borderline personality disorder to further clarify the role of biology in this psychiatric problem. ■

Six Additional Centers Using New Experimental Cancer Treatment

Florence S. Karlsberg

The National Cancer Institute (NCI) has announced that six medical centers will begin treating advanced cancer patients within the next two months with the experimental immunotherapy developed at the NCI by Steven A. Rosenberg, M.D., Ph.D., and his colleagues. An estimated 300 patients, about four per month at each center, will be treated during the year.

The six centers that will participate in administering the treatment will each receive approximately $500,000 from the NCI to conduct this research. They are the New England Medical Center, Boston; Montefiore Medical Center/Albert Einstein College of Medicine, New York; Loyola University Medical Center, Maywood, Illinois; University of Texas Health Science Center/Audie Murphy V.A. Hospital, San Antonio, Texas; Cancer Research Institute, University of California, San Francisco; and the City of Hope National Medical Center, Duarte, CA.

The NCI research team reported in December 1985 that this new immunotherapy successfully activated the immune system to destroy cancer cells in 11 of 25 patients with advanced cancers. The new therapy combines an immune system activator, interleukin-2 (IL-2), with a unique population of killer cells, known as LAK cells. The LAK cells are generated in the laboratory after removing a patient's white blood cells with a special machine and then treating the cells with IL-2. The scientists infuse these LAK cells, along with IL-2, back into the patient. The IL-2 induces the LAK cells to multiply for a short time in the body, thus enhancing their ability to destroy cancer cells (but not normal cells).

Approximately 50 patients with advanced cancers will be treated with the LAK/IL-2 treatment at each center. Since this therapy appears to be most effective against melanoma, colon, and kidney cancers, patients with advanced stages of these cancers will be eligible for the trials at the six centers.

In response to intense public interest in this new treatment, the NCI invited cancer research institutions to submit proposals for clinical trials that would use the new immunotherapy approach to confirm Dr. Rosenberg's findings. An NCI committee reviewed the proposals that had been submitted. This committee included staff of the Cancer Therapy Evaluation and the Biological Response Modifiers Programs. The most promising applicants received letters asking for further clarification of specific parts of their proposals. The participating centers were selected because of: their history of competence in conducting Phase I clinical trials that use aggressive approaches to determine the safety and maximally tolerated dose of an anticancer drug; history of animal or human research with either IL-2 or LAK cells; willingness to repeat Dr. Rosenberg's study design; ability to accrue the required number of patients; the commitment of their intensive care units to perform this demanding procedure; and ability to mobilize quickly to perform this highly specialized procedure requiring an active immunology laboratory.

Scientists at the NCI Surgery Branch, Division of Cancer Treatment (DCT), Bethesda, and at the Frederick Cancer Research Facility (FCRF) in Frederick, Md., have been able to treat only four to eight patients per month because of the complexity of this treatment. Currently they are accepting only selected patients with advanced kidney cancer or malignant melanoma. The additional six centers are accepting patients with advanced melanoma, colon or kidney cancers that have responded poorly to standard therapy. ■

Study Finds No Link Between Breast Cancer and Oral Contraceptives

Patricia Blessing

Young women who have used oral contraceptives are at no greater risk of developing breast cancer than are women who never used birth control pills, according to a new study that appeared in a recent issue of *Lancet*.

"Until now, concern has been raised about the possibility of pill use leading to an increased rate of breast cancer in young women," said Dr. Bruce Stadel of the National Institute of Child Health and Human Development (NICHD). This is the first report from the Cancer and Steroid Hormone Study that looks specifically at the relationship between oral contraceptive use and breast cancer that develops at an early age.

NIH PHOTO 2127

In the United States, the birth control pill is the second most popular method of contraception, next to sterilization. About 70 percent of all women have used oral contraceptives at some time during their reproductive years.

The study explored several factors suspected of influencing the risk of breast cancer among pill users: how old the women were when they started using the pill, how long they used it, the amount of the hormone progestogen in birth control pills, and whether they used the pill before having their first child.

Dr. Stadel and researchers at the Centers for Disease Control (CDC) selected 2,088 women between the ages of 20–44 who were diagnosed with breast cancer between 1980 and 1982. These women, who lived in eight different areas in the United States, were compared to 2,065 women of similar ages, selected from the same areas, who did not have breast cancer.

To find out which women used oral contraceptives, at what age, and for how long, trained specialists interviewed the women in their homes. The interviewers used pictures of the different types of oral contraceptive packages to help the women who used the pill recall the brand and dosage they used.

Regardless of the age at which the women started using the pill or how long they used it, the researchers found that there was no greater risk of breast cancer compared to women who never used birth control pills. In fact, the birth control pill neither raised nor lowered the risk of breast cancer even when the women started using the pill before the age of 20 and continued to use it for more than four years, Dr. Stadel said.

Two other issues, the use of high progestogen pills and use of the pill before having a first child, were examined because they formed the basis for two reports published in late 1983 that rekindled the debate over the link between the pill and breast cancer in young women.

Since the results of these studies have been controversial and some scientists questioned their validity, Dr. Stadel and his colleagues looked at these issues very carefully. He added that the Cancer and Steroid Hormone Study is one of the most thoroughly designed studies ever performed on this topic and avoids many of the flaws identified in previous studies.

In this new study, Dr. Stadel said that even when women used high-progestogen pills for more than six years before age 25, they had no greater risk of developing breast cancer than did women who never used birth control pills.

Among the women who used the pill for more than four years before the birth of their first child, the researchers found no greater risk of breast cancer than among non-pill users.

"We now have a good deal of confidence that pill use does not affect young women's risk of breast cancer," Dr. Stadel said. And since most of the know risks from the pill are related to cardiovascular disease, which is rare among young women, he concluded that "the pill appears to be a safe method of birth control for most young women who use it." ■

Laser Treatment Reduces Vision Loss in Diabetics With Macular Edema

Margaret Strock

Results from a multicenter clinical trial—supported by the National Eye Institute (NEI)—have shown that treatment with a laser can reduce the risk of visual loss from diabetic macular edema by 50 percent.

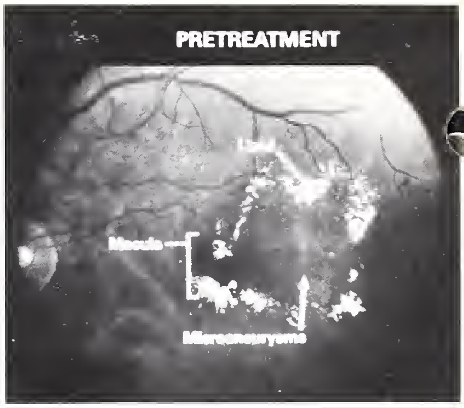
At a recent press conference held in Washington, D.C., AMA President, Harrison Rogers, M.D., said, "Diabetes is responsible for loss of vision in thousands of Americans each year. In 1976, laser photocoagulation was shown to be effective in preventing severe visual loss from advanced proliferative diabetic retinopathy. This new study shows that laser photocoagulation also is effective in preventing loss of vision from diabetic macular edema," a somewhat less severe condition that nonetheless can have a profound effect on the quality of life.

In diabetic macular edema, vision is blurred by excess fluid which swells retinal tissue. While visual loss from macular edema is not as severe as that from proliferative diabetic retinopathy, it can be serious enough to keep an individual from performing such everyday functions as reading and driving a car.

Enrolled in the study were people whose eyes were in the early stages of diabetic eye disease. A total of 1490 eyes were assigned to the deferred treatment group while 754 received immediate focal photocoagulation with the argon laser. After three years of follow-up, 24 percent of the eyes in the untreated group had lost a significant amount of vision, while only 12 percent of those in the treated group had done so. And, while laser treatment increased the likelihood of an improvement in vision and decreased the frequency of persistent macular edema, it caused only minor visual field changes.

The focal photocoagulation technique evaluated in the study coagulates only the blood vessels in the macular area suspected of leaking fluid into the macula. This technique differs from the panretinal technique used in treating proliferative diabetic retinopathy in which many laser burns are placed in the peripheral retina, avoiding the macula.

The new findings, from the Early Treatment Diabetic Retinopathy Study, were published in a recent article of the AMAs *Archives of Ophthalmology* and in an editorial in Journal of the American Medical Association *(JAMA)*. Thus 18,000 ophthalmologists and almost 150,000 primary care physicians were reminded of the necessity of yearly eye examinations for their diabetic patients. ■



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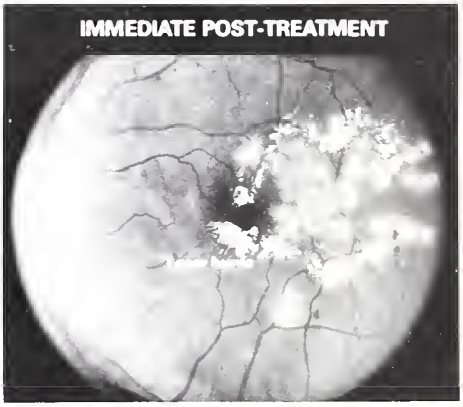

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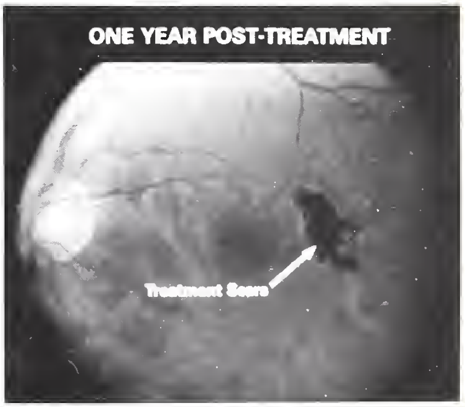


NIH PHOTO 2130

Individuals with diabetic macular edema suffer from visual loss due to fluid that swells in the retinal tissue. Many must curtail their daily activities, including driving and reading. NEI researchers have found that when these individuals undergo laser photocoagulation—the process shown in the photos above—their vision improves as a result of the treatment. The technique involves coagulating only the blood vessels in the macular area that are leaking fluid into the macula. Of those individuals that were untreated, 24 percent lost a significant amount of vision, while only 12 percent of those who were treated had done so.

Basic Research Reveals Structure of Cold Virus

Doris Brody

Although science is still a long way from finding a cure for the common cold, researchers recently took an important step toward understanding how cold viruses work. Michael G. Rossmann, Ph.D., a National Institute of General Medical Sciences (NIGMS)-supported scientist working at Purdue University in West Lafayette, Indiana, announced that his laboratory had solved the structure of one of the many viruses known to cause colds in humans. Dr. Rossmann has been supported by the NIGMS for over 20 years for structural studies of proteins and other molecules. The work on the cold virus itself was funded by the National Institute of Allergy and Infectious Diseases (NIAID).

The successful study of the cold virus by Dr. Rossmann, a pioneer in developing and refining methods to determine molecular structure, is an excellent example of the eventual payoff from years of painstaking basic research. Before the highly complex viral structure could be tackled, the necessary tools had to be developed. Much of this work was accomplished through studies of simpler protein structures.

Proteins are vital to every biochemical event that keeps cells alive and functioning. Specialized proteins also form the structural features of cells and confer resistance to disease. Proteins vary markedly in shape and size, and may contain anywhere from 50 to thousands of smaller amino acid molecules. An important first step in understanding a protein is to determine the sequence of its amino acids. Automated protein sequencing now makes this job much faster and easier.

A protein's sequence does not reveal its complete structure, however. The amino acid chains coil and fold into complex three-dimensional shapes that determine the molecule's function. X-ray crystallography, the same technique that 30 years ago provided information crucial to the solution of DNA structure, is the chief method of collecting the data from which to determine molecular structure. Because single molecules may not provide a good image of the arrangement of their atoms, crystals which hold many molecules in identical orientation and in regularly spaced positions are used. X-rays passed through the crystals are diffracted by atoms in specific patterns from which the three-dimensional arrangement of the atoms can be calculated—a very time-consuming process.

Structural studies often provide specific information about how biological molecules function. For instance, many proteins perform their functions only after some structural feature on the protein recognizes and binds to a complementary feature on another molecule. Often described as a lock-and-key relationship, this binding would not take place if the structural feature—that is, the binding site—is altered.

Rhinovirus 14, the cold virus studied by Dr. Rossmann, is a thread of genetic material surrounded by a protein shell. The structure of the shell determines how the virus attaches to a cell and also how the body's defense system is eventually able to defeat it.

Once the virus binds to the cell, it drops its protein coat and the genetic material enters the cell where it directs the production of more viruses that then leave the cell and go on to infect other cells. Meanwhile, antibodies, the body's defense against invasion by foreign substances, seek out and attempt to neutralize the intruder. These antibodies work by recognizing a site on the viral protein coat and binding to it. Scientists believe that antibodies may stop cold viruses by distorting the shape of the portion of the virus that attaches to the cell.

Prior studies of the cold virus showed it to resemble a fuzzy, multifaceted ball. The new, much more detailed studies reveal that the virus' complex protein shell is composed of triangular surfaces having irregular peaks and valleys. Dr. Rossmann's group, in collaboration with a team of researchers headed by Dr. Roland Reuckert at the University of Wisconsin, has identified four sites on the viral surface that host antibodies can recognize and attack. They believe that the part of the shell that must attach to a cell to cause infection lies well protected within a deep cleft. The antibodies that eventually halt a cold infection may bind to sites on the rim of the cleft.

A balsa wood model of the electron-density map showing the external portion of the cold virus. (Photo courtesy of Dr. Michael G Rossmann, Purdue University).

NIH PHOTO 2131

In order to map the viral structure, Dr Rossmann's group collected about 6 million pieces of information gathered from hundreds of X-ray diffraction photographs of the crystallized virus. The final set of computations to analyze this information was made in about one month, but might have taken 10 years without a supercomputer, called the Cyber 205, which can speed up calculations a hundred times or more. Most of the data analyzed by the computer were collected with the aid of the Cornell high energy synchrotron, an atomic particle-smashing machine used by physicists to study novel subatomic particles. As a byproduct the synchrotron generates X-rays at least 100 times as intense as those produced in a conventional laboratory, thus creating much better X-ray diffraction pictures.

Determination of the viral structure is an important step, but it will not lead immediately to a cure or prevention for the common cold. Since each one of the many cold viruses requires a unique set of antibodies to control it, preventing colds could require 100 or more different vaccines. Producing some sort of an antibody to the cleft, which may be similar in the various cold viruses, seems unlikely because it is especially deep and probably inaccessible. However, antibodies to sites on the rim of the cleft could be produced. Researchers also see the possibility of several nonimmunological approaches—perhaps ones that would be of use in fighting more than one type of cold virus. For instance, scientists might be able to design something that would prevent the virus from being able to shed its protein coat or from assembling the coat, two steps that are essential for the virus to be able to infect cells successfully.

Dr. Rossmann and his colleagues are now using the Cornell synchrotron to study in three dimensions the relationships between the cold virus and substances that may bind to it. This information could lead to the design of novel antiviral drugs. In addition, knowledge of the architecture of this very large and important virus opens the door for many other experiments, both with this and other viruses. ■

BIOTECH BLURBS

Mail-Order Genes: Human DNA Warehouse Established in Rockville

By the end of the next decade, DNA segments representing the complete set of human genes may reside at a repository located in Rockville, Maryland. The repository will be a central warehouse where copies of human DNA segments, called probes, can be collected, stored and distributed to scientists around the world.

Presently, about 1,000 well-studied probes are available for entry into the repository, and this number is expected to double each year. The repository will enable scientists to locate and easily acquire small pieces of human DNA to study and diagnose genetic diseases.

"Practically every aspect of human genetics has been revolutionized by the use of DNA probes," said Dr. Jeanette Felix, a National Institute of Child Health and Human Development (NICHD) consultant in genetics. Dr. Felix will approve entry of probes into the repository, established through a $1.5 million contract from NICHD to the American Type Culture Collection (ATCC) in Rockville.

DNA probes have become valuable molecular tools for genetic researchers to locate genes on specific chromosomes, reproduce identical copies, and distinguish normal from abnormal genes. Already geneticists have used probes to determine before birth if an infant will inherit certain genetic diseases, such as phenylketonuria (PKU) which causes severe mental retardation if not treated. More recently, DNA probes were used to locate a genetic marker for cystic fibrosis providing the first clue in finding the defective gene responsible for the deadly disease. (See story in this section).

Probes take advantage of the structure of DNA, which resembles a twisted ladder. The rungs of the ladder consist of bases called nucleotides that always pair with a specific complementary partner. A probe is like half of the ladder—a single strand of bases without their partners.

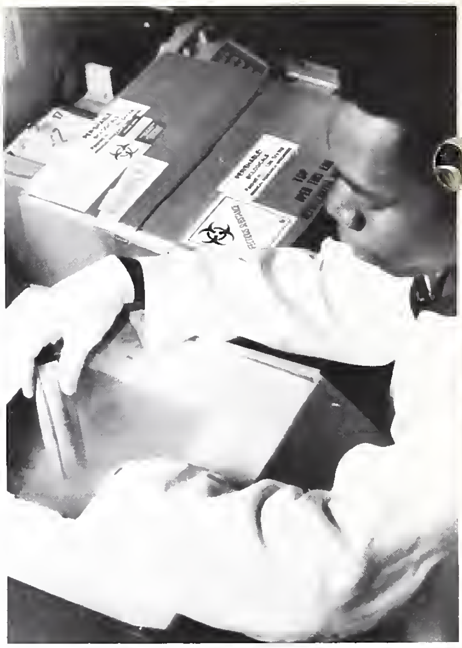
Scientists can tag probes with radioactivity, and mix them with DNA of cells they are studying. First, they expose the cell's DNA to high temperatures or harsh chemicals, so the ladder rungs split, and the ladder unwinds. Then, the scientists can easily study the hybrid DNA to detect where the tagged bases on the probe match up with complementary bases on the cell's DNA.

The fast-paced technologies of molecular biology have greatly enhanced researchers' ability to reproduce or clone DNA. One of the most popular applications of cloning is to manufacture in bacteria replicas of normal or mutant base sequences. Using these probes, for example, scientists identified the gene responsible for making human growth hormone. By using recombinant DNA techniques, researchers are now making billions of copies of this gene and using the protein it makes to treat certain growth hormone deficiencies.

Human DNA contains 6 billion base pairs, and probes can range anywhere from 20 to 50,000 base pairs long. Because probes usually do not represent one entire gene (sometimes only part of a gene or two genes overlapping), the number of probes possible for the entire human genome is staggering.

So as each new probe enters the repository, a complete history will be filed in a computer storing such information as how many bases the probe contains and how it was made. By using a computerized "mail-order catalogue," gene researchers can obtain information and purchase human DNA sequences for diagnosis or research.

DNA segments, spliced with the genes of living bacteria, are freeze-dried and stored in small vials. The vials are preserved under subfreezing temperatures in refrigerators that are automatically supplied with liquid nitrogen (-196 C, -320F). When a scientist orders a probe from the repository, new copies of the genetic material are made by thawing the sample and allowing the bacteria to multiply (Photo courtesy of the American Type Culture Collection). NIH PHOTO 2132



A technician packs the genetic material in dry ice to preserve the specimen during shipping (Photo courtesy of the American Type Culture Collection). NIH PHOTO 2133

In addition, researchers at the Los Alamos and Lawrence Livermore National Laboratories, who are developing a gene library for each of the 24 pairs of human chromosomes, will transfer their libraries to the ATCC for storage and distribution. Each segment of DNA from any given chromosome will represent a "book" in that chromosome's library. The Division of Research Resources (DRR) at NIH will cover the cost for transferring these libraries to the ATCC.

"The main advantage of having both the libraries and the probe repository at the same place is that they will complement each other," Dr. Felix said. For example, a researcher who has made a probe can search each chromosome library to pinpoint which chromosome or gene the probe seeks out. Or the researcher who is studying a particular chromosome can start out in a library, and make a DNA probe from a known gene segment located on that chromosome. ■

Patricia Blessing

Scientists Identify Genetic Marker Linked to CF Gene

The recent discovery of a genetic marker nked to cystic fibrosis (CF) has provided ew impetus to the search for the underying cause of CF, the most common lehal genetic disorder among Caucasians. Researchers at Toronto's Hospital for Sick Children, including Dr. Lap-Chee Tsui—a scientist supported by the Naonal Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDK) and Collaborative Research in Boston have reported the identification of a segment of DNA that is linked or transmitted with the CF trait in 85 percent of cases—a discovery that is the first step in identifying the gene that causes CF.

CF is the most common genetic disorder n Caucasian children. About 10 million Americans carry the CF gene and about in 2000 newborns have CF. CF victims uffer from chronic life-threatening lung nd digestive problems. The pattern of nheritance suggests that CF might be he result of defects in a single gene. Depite extensive research, the basic moecular defect in CF remains unidentified.

n diseases such as CF, where little is nown about the genetic defect that auses the disease, restriction fragment nalysis may be useful. Individuals show ariations in how their DNA is cut by cerain restriction enzymes, just as they have ecific blood groups. These variations re not significant, but provide valuable nformation when, by chance, a particular attern is caused by differences close to he disease-causing gene. When this ocurs, it may be possible to track the abormal gene by following the restriction agment pattern. This technique is called nkage analysis, indicating a physical nkage between the identifiable marker nd the trait.

cientists do not believe that most geetic diseases will be diagnosable by iscovering a direct correlation between known mutation in the gene and a reriction site, because the nature of the NA mutation in most genetic diseases is nknown. Restriction fragment length polmorphisms (RFLPs) can be useful in ese cases. Restriction enzyme sites are e specific sequences in DNA at which ne of the known restriction enzymes recgnizes and cuts the DNA molecule. enerally, specific enzymes cut the DNA to fragments of characteristic length. If, owever, the sequence of nucleotides is bnormal at the point where the enzyme ould cut, the enzyme will not cut there ut at the next enzyme site, producing a NA fragment of unusual length. In this ay, a DNA variant can be identified and ked with a genetic disease. When such linkage exists between an abnormal ene and a DNA polymorphism, the oser the restriction enzyme cutting site to the gene, the more likely it is that ey will be inherited together.

In this study, the scientists isolated more than 200 new RFLP DNA markers and found that one is indeed linked to the CF gene. DNA samples from thirty-nine CF families were analyzed, indicating a linkage between the marker and the disease. Based on its location, the discovery of the DNA marker narrows the search for the CF gene to one percent of the human genome.

One of the possible applications of a DNA marker is in diagnosis. However, this particular marker is "located" too far away from the CF gene for this application, but it does pave the way for the discovery of other gene markers closer to the CF gene. Perhaps, even more importantly, it is a major initial step to understanding how this disease causes its lethal effects and how it can be treated more effectively.

This study was reported in a recent issue of *Science*. ■

Charlotte Armstrong

DNA Clone May Provide Key to Tay-Sachs Disease

An intramural scientist of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDK). Dr. Rachel Myerowitz and her colleagues have reported the isolation of a DNA clone (copy of a gene) containing the entire coding sequence for the alpha-subunit of a degradative enzyme, beta-hexosaminidase. This genetic probe will help in the identification of the mutations that cause Tay-Sachs disease in Jews of eastern European extraction (Ashkenazi) as well as other affected individuals.

Mutations in this gene—and resultant defects in the alpha-subunit of the enzyme—lead to Tay-Sachs disease, a rare, devastating genetic disorder that causes buildup of fatty deposits in the brain, leading to early death. Ashkenazi Jews are at 10-fold higher risk for the disorder than the general population. Studies have shown 1 in 30 Jewish individuals to be carriers of the disorder.

In this study, the scientists isolated a cDNA clone containing the entire coding sequence of the alpha-subunit and used it as a probe to determine the presence of mRNA (messenger RNA, the genetic material that directs protein synthesis) in the cells of an Ashkenazi patient with Tay-Sachs disease and in two controls. cDNA or complementary DNA is a synthetic single stranded DNA molecule that is complementary to a specific mRNA molecule and is synthesized from it. cDNAs are important laboratory tools for isolating and studying individual genes. It is easier to detect a protein's mRNA among cells or tissue samples than the protein itself. Previously, Dr. Myerowitz and NIADDK scientist Dr. Richard Proia reported the isolation of a smaller DNA probe for the alpha-subunit.

Using the probe, the scientists report that the cells from the Ashkenazi patient were found to be deficient in the mRNA needed to synthesize the entire B-hexosaminidase alpha subunit. "Now that we have found the entire coding sequence of the gene for Tay-Sachs, we can look at the abnormal genes, particularly in the Ashkenazi Jewish population and determine the genetic lesion causing the disorder," state Dr. Myerowitz.

The research was reported in a recent issue of the *Proceedings of the National Academy of Sciences*, U.S.A ■

Clementine Sessoms

Scientists Capture Elusive Reproductive Protein—May Provide Basis for Male Contraceptive

Using genetic engineering techniques, scientists have isolated and characterized a protein that appears to block a hormonal step necessary for the development of sperm and egg cells. Because the protein, called inhibin, blocks this step without upsetting the body's hormonal balance, it may lead to improved birth control pills for women and provide the basis for a hormone contraceptive for men.

Inhibin may also "constitute a missing link" in knowledge about the mechanism that precisely orchestrates secretion of reproductive hormones, according to endocrinologist Dr. Roger Guillemin, a scientist supported by National Institute of Child Health and Human Development (NICHD) at the Salk Institute in La Jolla, California.

Guillemin, his colleagues at Salk and those at the biotechnology firm Genentech, Inc., in South San Francisco, have reported their findings in a recent issue of *Nature*.

Although scientists have suspected for many years that both male and female sex glands make a substance like inhibin, isolating the protein and describing its structure had to await the development of modern gene splicing techniques. Using DNA clones obtained from gene libraries and restriction fragment analysis, scientists have identified the entire structure of inhibin, which allows them to study exactly how the protein blocks reproduction.

"Endocrinologists have postulated the existence of an inhibin since the '30s," says Dr. William Sadler, Chief of NICHD's Reproductive Sciences Branch. "But this has been based on indirect evidence. Now we can supply inhibin to researchers who will test to see if it really does what we thought it would do."

A half-dozen or more hormones secreted at different times from the ovaries or testes and regions of the brain perform a delicate balancing act that controls reproduction. By adding or taking away these hormones, scientists developing oral contraceptives have tried to tip the balance, disrupting the chain of events that leads to the growth and discharge of eggs or sperm.

"Discovering the structure of inhibin is attractive from a practical point of view because of its potential as a contraceptive," says Dr. Sadler. "This discovery could provide a basis for the first hormone-based male contraceptive."

In both women and men, for example, the pituitary hormone FSH stimulates the sex glands to produce eggs or sperm. By blocking FSH secretion, inhibin may indirectly prevent the ovaries or testes from producing sex cells.

But inhibin would differ from other hormone-based contraceptives, because it appears to block fertility without disturbing the rest of the body's hormonal balance. Because of their overall effects on the hormone system, current birth control pills produce side-effects that prevent some women from using them. And although scientists have previously tested FSH-inhibiting substances as male contraceptives, their unwanted side-effects have kept them off the market. These drugs effectively blocked FSH secretion—and thus, sperm production—but, they also blocked the pituitary's secretion of LH, a reproductive hormone that indirectly controls sex drive in men.

"You've got to develop a substance that won't inhibit LH, too," says Dr. Sadler. "Because if you inhibit LH, you won't get any men to take the drug."

Inhibin may overcome these obstacles for both men and women by acting only on FSH-producing cells of the pituitary gland. In this way, it may block fertility without disturbing the amount of LH or other reproductive hormones.

While knowledge of the molecular structure of inhibin will help scientists learn how to use the substance safely as a contraceptive, it will also help them learn more about how hormones in both sexes control reproduction. During a woman's monthly cycle, for example, the secretion of FSH is precisely timed to occur when LH levels are low. Although they do not fully know the mechanism that controls these changing hormone levels, scientists suspect that inhibin helps coordinate their rise and fall, which is essential for normal reproduction. ■

Leslie Fink

Sequencing the Human Gene for Interleukin-2—Receptor Provides New Tool for Studying Leukemia and Immune Diseases

A team of scientists has determined the structure of the gene encoding the receptor for interleukin-2 (IL-2), an essential chemical of the immune system that helps immune (T) cells multiply. This information has made possible the study of IL-2 receptor synthesis, which has been shown to be abnormal in immune cells from patients with a rare virus-caused leukemia.

"We hope our results will increase our understanding of uncontrollable T cell growth in this form of leukemia" said cell biologist Warren Leonard of the National Institute of Child Health and Human Development (NICHD), a member of the research team that reported its findings in a recent issue of *Science*.

When viruses and other organisms infect T cells, they stimulate them to produce IL-2. This substance then seeks out and binds to other T cells carrying IL-2 receptors on their surfaces. Binding to the receptor sets up a chain of events that causes T cells to multiply, increasing their attack on invaders.

Because IL-2 helps T cells grow and multiply, it is also known as T cell growth factor. Defects in the gene or the receptor it encodes may disrupt the series of events that leads to normal cell division. And too many or too few T cells in the blood can cripple the immune system.

Patients infected with the cancer-causing virus HTLV-1, for example, produce a large number of leukemic T cells, which appear to bear 5 to 20 times the number of IL-2 receptors, as do normal T cells exposed to other disease-causing agents.

Starting with the gene, Leonard and his colleagues followed the steps a cell must take to make the IL-2 receptor—a protein molecule made up of three distinct segments. They then compared the receptor protein in both normal T cells and those infected with HTLV-1.

When looking at the IL-2 receptor, the scientists found no differences between normal and cancerous (HTLV-1) T cells. But when they compared the steps these two types of cells take to control the number of receptors they produce, the researchers found in the cancer cells an alteration in one of the steps.

During protein synthesis, enzymes copy the genetic material, DNA, into messenger RNA (mRNA)—the blueprint for protein. Signals along the DNA molecule tell the enzymes where to begin copying DNA to mRNA.

While most genes contain only one copying signal, normal IL-2 receptor genes contain two. The scientists found that these genes in HTLV-infected T cells contained three mRNA-producing signals, which seem to cause the cells to make extra receptors.

"There is a lot of interest in why there are extra signals in some genes," says Leonard. "Uncovering such a signal implies there is something abnormal about the way leukemic T cells regulate IL-2 receptor synthesis," which may play a crucial role in the development of these cells." ■

Leslie Fink

MEDICAL CAPSULES

Sandra D. Levine

Corneal Transplant Study Tests Immunosuppressive Drug

The first clinical study to test cyclosporine's ability to combat graft rejection n corneal transplant patients is being conducted by the National Eye Institute NEI) and the Louisiana State University (LSU) Eye Center. Researchers also will nvestigate if this immunosuppressive drug, that has been used successfully in preventing rejection in other organ transplants, will cause fewer harmful side-effects than steroids in corneal transplant patients who are at high risk of graft reection because of previous failures. All 100 patients in the study will use steroid eyedrops. Half will receive standard reatment with oral steroids as well, while he other half will receive oral doses of cyclosporine. Investigators will then evaluate the safety and efficacy of the two reatments. The researchers are interested in patients who have had at least [illegible] previous corneal transplants that [illegible]ed, or one failed graft in the presence f corneal problems in both eyes. Addional information on this study is available from NEI at (301) 496-3123 or from LSU at (504) 568-6700.

Satellite Conference Links U.S. and Soviet Cardiologists

A unique medical conference that linked American and Soviet cardiologists via satellite took place recently at the Naional Library of Medicine's Lister Hill Center.

Seven of America's leading heart specialsts, including bypass surgery pioneer Dr. Michael DeBakey, discussed the Present Status of Prevention and Treatment of Coronary Heart Disease" with five Soviet experts from the National Cardiology Research Center in Moscow.

The topics included coronary bypass surgery, coronary arteriosclerosis, medical reatment of heart disease, and how both countries are fighting coronary artery disease.

The joint conference, MEDICOM '85, was an attempt to enhance cooperation and nformation exchange in the field of medicine between the U.S. and U.S.S.R., as [illegible] outgrowth of the Geneva summit.

Pollutant Levels Decline with Breast-Feeding

Studies supported by the National Institute of Environmental Health Sciences (NIEHS) on two important environmental pollutants have found that the levels of these chemicals were lower in women who had breast-fed previously, and that the levels declined substantially over the course of breast-feeding and with the number of children nursed.

Studies conducted as early as 1951 had shown detectable levels of both polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE—a metabolite of DDT) in the breast milk of women. The new NIEHS study of 868 women is one of the very few studies in which women were followed over time.

Levels of DDE were found to be elevated in older women, black women, cigarette smokers and women who ate sport fish. Whereas there were substantial racial differences in DDE levels—almost 50 percent of the black women had levels above 6.0ppm compared with only 5 percent of the white women—levels of the environmental pollutant PCB showed no differences by race. PCB levels, like those of DDE, appeared to rise with age (up to 30 percent higher). Elevated PCB levels were also found in women who consumed at least one alcoholic drink per week during pregnancy (13 percent higher levels) and in those with no prior pregnancies (11 percent higher levels).

The study, reported in a recent issue of the *American Journal of Public Health*, indicates that the presence of PCBs and DDE in the body is attributable to widespread low-level contamination through food, and skin or lung absorption. However, no major health problems have been reported as a result of these chemicals at currently existing levels.

Study Reveals Risk Factors for Alzheimer's Disease

Results from the largest case-control study of Alzheimer's disease to date have revealed risk factors associated with this disorder. The three-year investigation by the Italian National Research Council, in collaboration with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), evaluated 116 cases in seven Italian research centers. For each patient with a clinical diagnosis of Alzheimer's disease, age- and sex-matched controls were selected from 116 hospital patients without dementia and from 97 individuals in the general population. Data from next-of-kin interviews revealed two factors significantly associated with Alzheimer's disease: history of dementia among (first and second-degree) relatives and birth to mothers after age 40. Head trauma was more common in cases than in either hospital or population controls, but the differences were not statistically significant. NINCDS scientists emphasize that this new evidence of familial aggregation does not necessarily mean that dementia is transmitted genetically. Other risk factors suggested by earlier studies, such as onset of thyroid disease prior to Alzheimer's or family history of Down's syndrome, were not corroborated

Seven-Year Diabetes Treatment Study Recruits Volunteers

A prospective study sponsored by the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDK) that could have a major impact on the future treatment of diabetes is recruiting 900 volunteers nationwide. The seven-year study known as the Diabetes Control and Complications Trial (DCCT) is designed to determine if precise control of blood glucose can prevent, slow or reverse some of the early complications of insulin-dependent diabetes. The DCCT is being conducted at 19 medical centers in the U.S. and two in Canada. The study will compare "standard" with "tight control" treatment of diabetes, and assign participants randomly to one of two groups. Standard treatment includes one or two insulin injections daily, self-testing of blood or urine, and a routine clinic visit every three months. "Tight control" includes administration of insulin by injection three or four times daily or by pump, self-monitoring of blood glucose levels, an initial hospital stay, and monthly clinic visits. Retinal changes will be the primary measure of development of complications. Participants must be between 13 and 39, have had insulin-dependent diabetes for one to 15 years, must not be taking more than two insulin injections per day or using an insulin pump, and must have no severe complications such as retinopathy, neuropathy, kidney disease or peripheral vascular disease. For further information, contact DCCT, Westwood Bldg., Rm 628, Bethesda, MD 20892.

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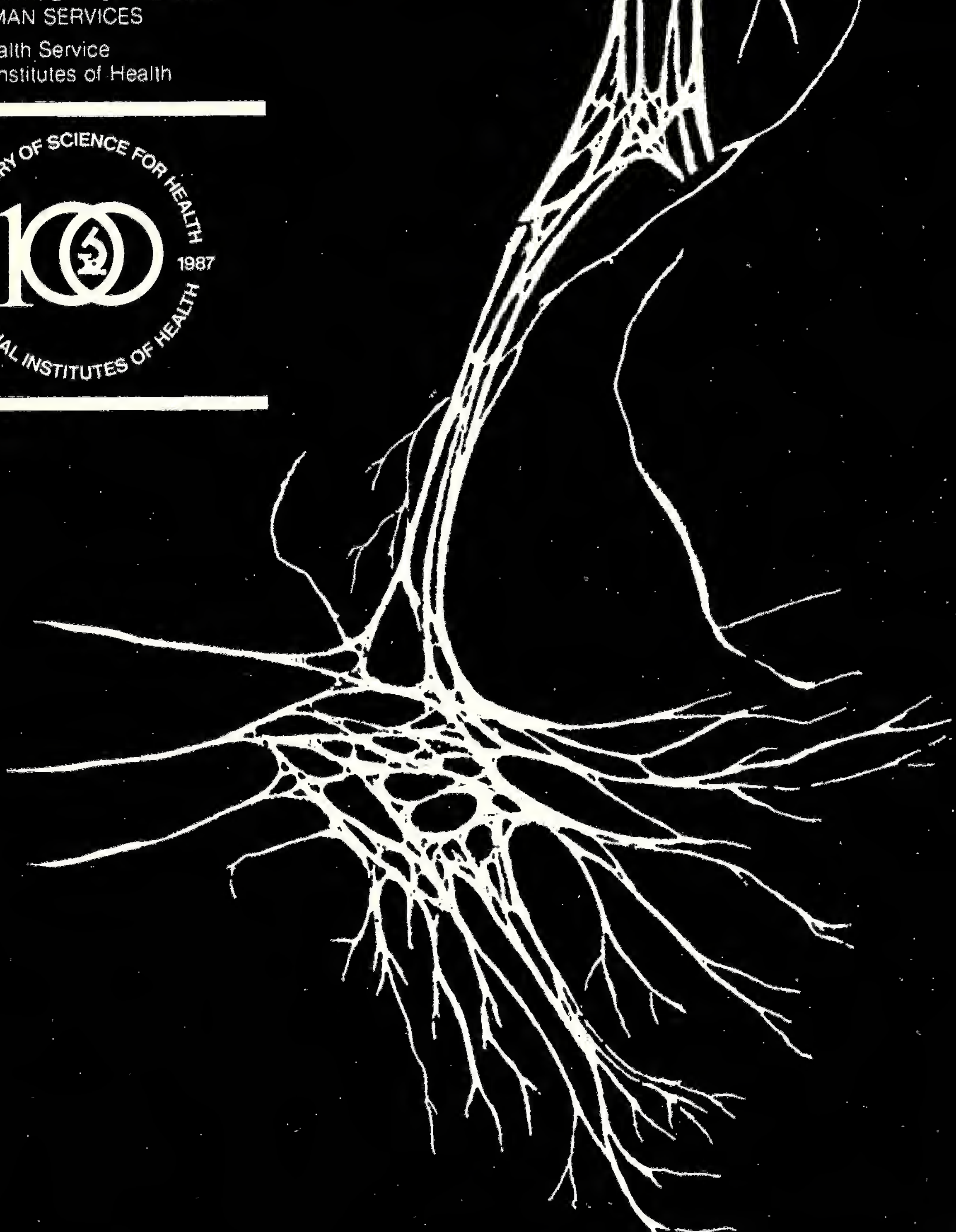
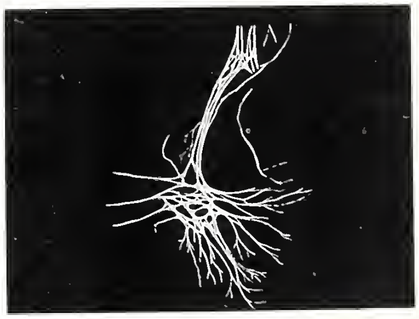


SPECIAL ISSUE—PAIN RESEARCH

Cover Photo: A neuron. Neurons carry pain messages from the site of an injury to the brain.



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The Pain Research Clinic at NIH

Pain is the most common symptom that causes people to seek dental or medical care and is one of the most difficult conditions to understand and treat.

To address this problem, in 1983 the National Institutes of Health (NIH) organized a coordinated attack on pain by opening the NIH Pain Research Clinic, the country's first pain clinic devoted exclusively to research. The Clinic is directed by the National Institute of Dental Research (NIDR), which has had a long-standing interest in pain since nearly one-fourth of all chronic pain problems occur in the oral-facial region.

The NIH Pain Research Clinic is a collaborative effort in which researchers and clinicians work together on studies of acute and chronic pain. Basic scientists study how pain messages are coded in the brain and how these messages can be modified. Their studies may eventually show us how we can control pain by activating our own internal pain-suppressing systems at will. Clinicians are developing new methods of diagnosing and assessing pain, and testing new methods of pain treatment. For the millions of Americans who suffer from painful conditions, the discoveries made by the NIH Pain Research Clinic offer hope for a pain-free life for everyone. ■

The NIH Pain Research Clinic is located in the Ambulatory Care Research Facility, the glass building on the right connected to the Warren Grant Magnuson Clinical Center, a 500-bed research hospital on the NIH campus.

Researching Pain at NIH

"Pain has an element of blank;
It cannot recollect
When it began, or if there were
A day when it was not."

—Emily Dickinson

Not a person alive can deny having experienced pain in one form or another.

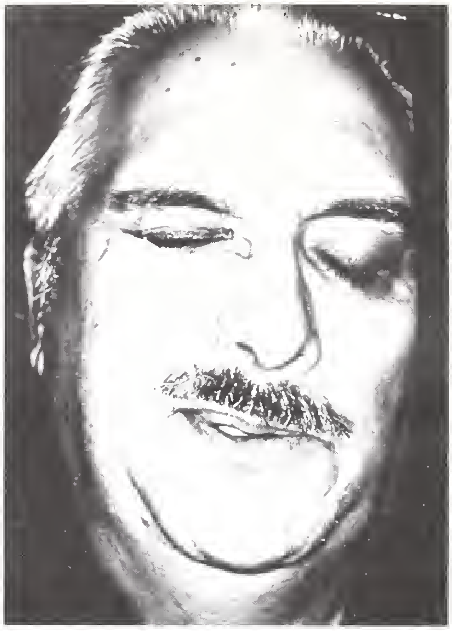
Whether it is the fleeting stab of a sharp pinprick, the incessant ache of lower back pain, or the endless throbbing of a headache, pain is a universal experience.

Our aches and discomforts, short-lived or continuous, are a link that binds all cultures and races. But why does pain occur? Can we eliminate pain? How can we measure something as subjective as pain?

In 1983, The National Institutes of Health (NIH) furthered the study of pain by opening the first multidisciplinary pain clinic in the United States devoted exclusively to pain research. Located in the Warren G. Magnuson Ambulatory Care Research Facility—an outpatient hospital on the NIH campus in Bethesda, MD—the Pain Research Clinic conducts studies that cut across all disciplines of science. Individuals suffering from a variety of pain problems are admitted as voluntary participants in research programs designed to improve the diagnosis, measurement, and treatment of acute and chronic pain. The Pain Research Clinic is a valuable resource that enables NIH researchers and clinicians to pool their knowledge and exchange ideas about the causes and treatment of pain. The knowledge generated by their expertise benefits pain patients everywhere as results of research studies are made available to physicians and dentists nationwide.

The Pain Research Clinic is directed by the National Institute of Dental Research (NIDR) which collaborates with other NIH Institutes to carry out pain studies. With an estimated 25 percent of all chronic pain problems occurring in the face and oral cavity, it is small wonder that the NIDR is the lead agency in pain research. Pain is one of the most common symptoms of oral and dental problems. It is also one of the principal symptoms that sends people to their dentists or physicians.

Chronic pain syndromes such as headache, cancer pain, arthritis, low back pain, and shingles cost the nation about $50 billion a year. And for pain patients, the adversity does not end with the financial burden; inability to work, sleeplessness, loss of appetite, depression, and withdrawal from social contact are symptoms that all too often result from chronic pain conditions.



Sudden stabbing episodes of pain characterize tic douloureux, a chronic pain syndrome. This patient was photographed during a typical attack.

The NIH Pain Research Clinic offers hope for these individuals. Under the direction of Dr. Ronald Dubner, chief of the NIDR Neurobiology and Anesthesiology Branch, basic scientists working in laboratories are generating new knowledge about pain mechanisms and pain control. Neuroscientists, neurologists, oncologists, dentists, pharmacologists, psychologists, and nurses apply this knowledge to patients seen at the Pain Research Clinic in the form of new treatments, new methods of assessing pain, and new understanding of the causes of some pain conditions.

Already, important discoveries have increased our understanding of the complex nature of pain. Scientists now know that the brain has its own systems capable of blocking pain signals. One day may be able to turn these systems off and on at will. Drug studies have validated the pain-relieving effects of many pharmacologic agents. Non-steroidal anti-inflammatory drugs combined with long-lasting anesthetics, for example, have been shown to provide excellent relief for pain that follows minor surgery such as the extraction of wisdom teeth. Anti-depressant drugs are proving to be effective pain relievers in conditions such as diabetic neuropathy and chronic facial pain. New ways to measure pain are standardizing the sensory and emotional qualities of pain. And experimental methods of pain relief, such as hypnosis, are also under investigation.

This special issue focuses on the many aspects of pain and the research studies ongoing at the NIH Pain Research Clinic. The collection of stories is representative of the broad spectrum of pain and the approaches that researchers and clinicians take in finding new methods of pain relief.

As valuable information is culled from pain studies, the ultimate goal of eliminating pain becomes a closer reality. Whether our pains are brief or long-lasting, the work accomplished at the NIH Pain Research Clinic benefits us all. ■

Understanding Pain

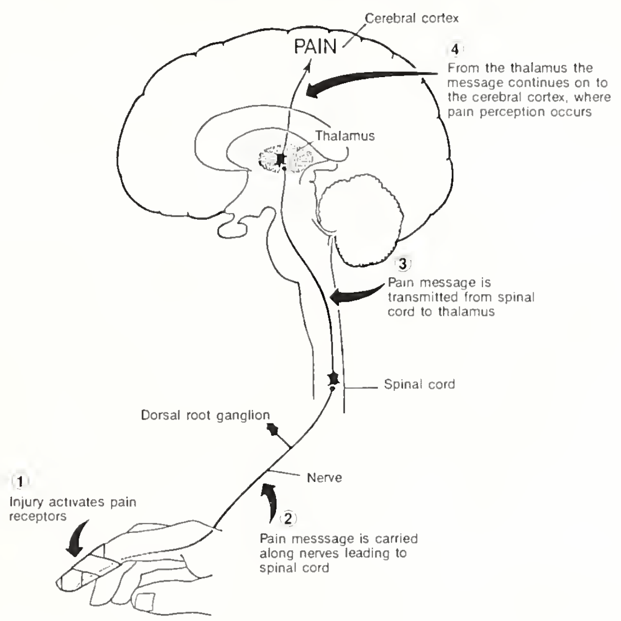
As scientists have long known, there is good pain and bad pain.

Good pain serves a useful purpose. A ankle that hurts, for example, may alert jogger to the possibility of a sprain. Or patient complaining of an ache in the lower right abdomen can lead a doctor t make a life-saving diagnosis of appendicitis. In these cases, the pain comes an goes with proper medical attention and the patient soon returns to a normal healthy state.

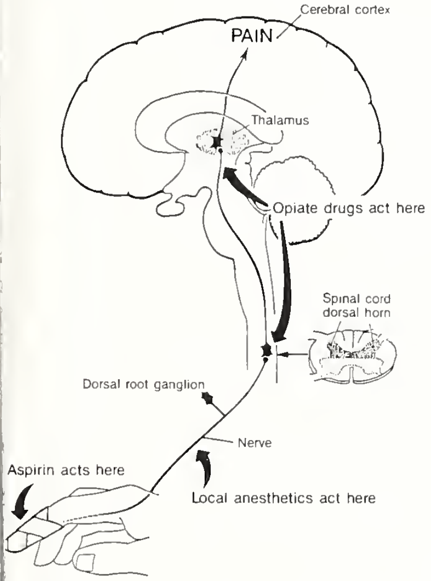
But for an estimated 40 million Americans, pain is a constant part of daily life. Nerve injuries, shingles, or cancer are just some of the conditions that can produce pain so chronic that people are unable to lead normal, productive lives. As basic scientists learn more about how pain signals travels through the body and how we can block pain through internal mechanisms, clinical researchers are able to apply their findings to help chronic pain patients.

Neuroscientists are now able to trace the intricate pathways that pain messages follow from an injured area up to the brain. The transfer of pain signals begins with specialized nerve endings,

Pain Pathways


Cerebral cortex
PAIN
4
From the thalamus the message continues on to the cerebral cortex, where pain perception occurs
Thalamus
3
Pain message is transmitted from spinal cord to thalamus
Spinal cord
Dorsal root ganglion
Nerve
1
Injury activates pain receptors
2
Pain messsage is carried along nerves leading to spinal cord

called nociceptors, contained in skin, muscle, and internal organs of the body. Nociceptors are sensitive to the various types of painful sensations that can occur. Some respond to several types of stimulation, such as a sharp blow, a drop [illegible] acid, or intense heat. Others are more selective and respond to a pinprick while ignoring painful heat or chemical stimulation. Nociceptors give information about the intensity of the pain and its location on the body surface.



hen an injury occurs, pain signals follow an scending pathway from the site of the injury o to the brain. Drugs are effective in relieving ain at different sites along the pathway. Asin, for example, works directly at the site of n injury. Local anesthetics relieve pain by inercepting pain signals that are traveling up e nerve. Opiate drugs are effective in the entral nervous system. They prevent the ansfer of pain signals from the dorsal horn to e brain.

When you accidently miss the nail and instead, bring the hammer down on your thumb, for example, nociceptors in the unlucky appendage send a barrage of nerve discharges into the central nervous system. The signals are transmitted by nerve fibers and carried to the dorsal horn, a layered structure in the spinal cord. The dorsal horn's own nerve cells then propel the pain signals up to the thalamus in the base of the brain. This transmission occurs through a release of chemicals called neurotransmitters that cause nerve impulses to be fired from one nerve cell to the next.

While pain signals move quickly up to the brain, other activities happen back at the site of the injury. Chemicals are secreted around the injured finger that result in inflammation. Hormonal substances called prostaglandins play an especially important role in the pain, heat, redness, and swelling that occur following an injury.

Interestingly, scientists now know why the proverbial "take two aspirin and call me in the morning" is such an effective prescription for countless aches and pains. Not only does aspirin block the formation of prostaglandins, thus reducing inflammation and pain, but inhibition of prostaglandins also decreases pain caused by other chemicals released following tissue injury.

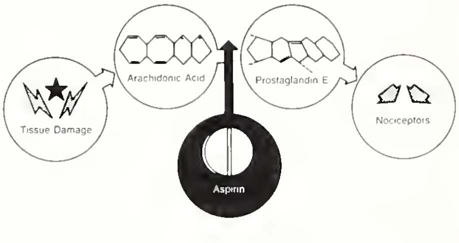
Over the last decade, pain research has focused on the body's internal methods of blocking pain messages. Just as we have distinct pathways that allow pain signals to reach the brain, we also have pathways descending from the brain that allow these signals to be modified or even totally blocked. Researchers have now isolated neurochemicals in the brain and spinal cord that operate in the descending pathways as pain-blocking agents. Called enkephalins, endorphins, and dynorphins, these families of opiate-like compounds occur naturally in our bodies.

For 2,000 years, drugs of the opiate family have been the most effective pain-relievers known to man. Opiate drugs are made from the juice of the poppy and have been used to treat ailments ranging from pain to shortness of breath, to congestive heart failure. Scientists now have shown that the naturally-occurring endorphins and enkephalins work on the same receptor sites in the brain as opiate drugs like morphine. When morphine is injected into the bloodstream, it mimics the effects of these naturally-occurring compounds.

Opiate drugs work differently than aspirin, however. Aspirin blocks pain directly at the site of an injury. Opiate drugs block pain signals that have already entered the central nervous system by preventing the transfer of pain signals from the dorsal horn to the thalamus.

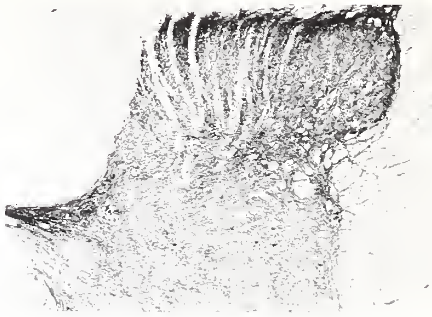
Certain stressful conditions can also activate the body's pain-suppressing mechanisms. A quarterback who continues playing with a broken leg or the wounded soldier carrying his disabled friend behind enemy lines are just some examples that show how stress can block pain and allow heroic feats.

TENS and acupuncture are other ways of switching on pain-suppressing systems. TENS is short for transcutaneous electrical nerve stimulation. In this procedure, small generators are attached to electrodes placed over the part of a patient's body that hurts. The electrical stimulation activates the body's pain-suppressing systems to block pain. Acupuncture is the ancient Chinese tradition of inserting fine needles at prescribed sites on the body to relieve a variety of pains. Like TENS, it does relieve pain in some cases by activating pain-suppressing systems, although neither



Aspirin is an effective pain-reliever because it prevents the formation of prostaglandins at the site of an injury. Prostaglandins are hormonal substances that play an important role in the pain, heat, redness, and swelling that occur following tissue damage. Prostaglandins also sensitize nociceptors—ne've endings—to painful stimulation.

Basic scientists contribute extensively to knowledge of the body's pain pathways. Dr. Ronald Dubner, Chief of the NIDR Neurobiology and Anesthesiology Branch, and Dr. MaryAnn Ruda, a senior investigator in the neuromechanisms section, examine a slide of spinal cord tissue sections to learn more about neurotransmitters in pain pathways.



This light microscopic photograph illustrates a cross-section of the spinal cord dorsal horn. The dorsal horn of the spinal cord receives pain signals from nerves and transmits them to the base of the brain.

TENS—or transcutaneous electrical nerve stimulation—may relieve pain in some cases. Small generators attached to electrodes are placed over the area of a patient's body that hurts. The electrical stimulation then activates the body's own pain-suppressing systems that block pain.

TENS nor acupuncture has proven helpful in patients with severe, progressive pain.

Much of our reaction to pain, however, is governed by our previous experience with it. Cultural background, a belief that medical help will work, and interestingly, the placebo response, all play a role. Some people, when given a placebo in an experiment—a pill containing no medication—actually do feel better because they believe that something is being done which will help them. The factors that influence individual reaction to pain are complex and cannot be explained by one pathway or one mechanism.

Researchers now are using what they know about the body's pain-suppressing mechanisms to develop drugs that work only on specific pain pathways without causing side effects. A major problem in combating cancer pain, for example, is that many of the opiate drugs currently used to relieve pain can also cause nausea, sleepiness, constipation, mood changes, and even slower respiratory rates. Cancer patients have the added problem of tolerance. Prolonged use of an opiate drug often requires periodic increases in dosage to keep patients pain-free. Eventually, patients may reach a point where the drug is no longer effective. Besides developing new drugs targeted only at specific pain pathways, scientists are developing drugs that work on different receptors in the brain, other than those sensitive to opiate drugs. If successful, these new drugs could be used to relieve pain when tolerance becomes a problem.

The intense study of pain pathways in the body and the search for natural pain-suppressing chemicals offer future promise for chronic pain sufferers and those who experience pain in the brief collision of thumb and hammer. Someday, we may learn how to turn on pain-suppressing systems at will and harness our innate ability to block pain. ■

The Impact of Chronic Pain

Dr. Mitchell Max (r.), Clinical Coordinator of the Pain Research Clinic, tests patient Bill Drake's reflexes during an examination to determine the distribution of nerve damage from diabetes.

"It started with a feeling of numbness in my toes, and a feeling that my shoes were uncomfortable. Everytime I stood, I felt like I was standing on rocks. Then it progressed to the point where I was getting extremely sharp pains, like somebody took a board studded with needles and raked it across the tops of my toes. First I would get one pain, and then another, and then another three or four seconds later. You never knew when it was going to strike. I almost got to the point where I wanted to have my legs cut off."

This vivid description is not science fiction. These are the words of Bill Drake, a 60-year-old Motorola Company executive who suffers from painful diabetic neuropathy. One of the more common chronic pain conditions—chronic meaning that the condition persists for a long period of time—diabetic neuropathy affects approximately one million people in the U.S. These are individuals with diabetes who develop nerve damage, particularly in their feet and sometimes in their legs and hands.

"When I first got it, I didn't even know what it was," recalled Bill. "I've had diabetes since I was 40, and the diabetic neuropathy didn't start until a couple of years ago. A podiatrist thought it was a problem with my shoes. I must have bought 15 pairs of shoes, trying to find relief. But the rocks were there all the time in my feet."

"I couldn't work in my garden, ride my bike, drive a car, or go for walks with my wife. My condition really kept us from being sociable. I didn't want to go out. If I was walking down the street and the pains came, I would stumble. If I was carrying on a conversation, I had to stop. The attacks would come everyday and I could count on it to happen, especially in the late afternoon or evening. That kind of thing really affects your spirit and your morale, and you find yourself not doing the things that you would like to do."

For Wanda Trollinger, a 45-year-old woman who suffers from diabetic neuropathy, the searing pain she felt in her legs prevented her from sleeping for months.

"During the day I was busy. I'm a high school English teacher and I have 160 kids sitting in front of me in my classes. I would tolerate the pain then. But when I went home I paid for it. There was no sleep—only this terrible burning sensation that started in my feet or my ankles, and then moved straight up through my legs."

"Sometimes the pains would last for hours. It got to the point where I couldn't walk. I had to miss vacations because my legs were so bad."

For both Bill and Wanda, relief has come in the form of a drug they received in 1984 while participating in the Pain Research Clinic's study of diabetic neuropathy. Called amitriptyline, the drug is actually an antidepressant used to elevate mood. Although some clinicians in private practice have also used amitriptyline for about 10 years to relieve chronic pain, a controlled group study was needed to validate the effectiveness of the drug. This was the study initiated by the Pain Research Clinic. During different phases, Bill, Wanda, and other participants received either amitriptyline or a placebo—a pill containing no real medicine. NIH researchers were able to provide evidence which suggests that amitriptyline provides pain relief separate from its ability to help depression.

"By the end of my first eight weeks in the NIH study, my pain disappeared," recalls Bill. "I knew I had been getting the real drug then. Even though it caused some side effects like sleepiness and dry mouth, it was worth it. Then during the second phase of the study I was sure that I was getting a placebo, because I was right back where I started with all the pain."

"During the study we had to keep a journal and write in it five times a day," added Wanda. "I had to describe what my mood was and what the intensity of my pain was, like "moderate," "severe," or "it's time to jump completely off the wall." The last six weeks of the study I definitely realized I was getting a placebo because my legs knew."

Today, Wanda and Bill are able to do all the things they want to do with minimal discomfort.

"I still have twinges in my legs when I've done too much, and sometimes my legs ache a little," says Wanda. "But amitriptyline is excellent medicine."

"I've been on a low dose of amitriptyline since the NIH study ended," reports Bill," and I've been fine ever since." "There is some numbness which is there all the time—if I walk barefoot I can't really feel my toes. But the difference is that I have no pain."

Confirmation of amitriptyline's ability to relieve pain at low doses provides a basis not only for treating diabetic neuropathy and other chronic pain conditions, but also may lead to new therapeutic approaches to pain management. Prolonged use of amitriptyline, for instance, is known to affect a variety of chemicals produced by the brain. Further study will attempt to identify which of these chemicals is related to the drug's pain-relieving effect. This will permit the development and use of drugs which produce analgesia without affecting other chemicals that result in side effects and drug toxicity.

NIH researchers believe the addition of amitriptyline to the growing list of drugs that can relieve pain may indeed be a breakthrough for individuals who suffer from diabetic neuropathy. ■

Bridging the Gap Between Research and Clinical Care

As basic scientists trace the body's pain pathways and learn more about how the pain system works on a cell-by-cell basis, clinicians apply this knowledge to pain patients in the form of new treatments and new drugs to relieve pain. But the relationship between basic research and clinical care is often obscure and misunderstood. The jump from laboratory to pain clinic can only be made after completing the tedious step-by-step process of biomedical research that requires years of study.

The process begins by developing an understanding of the underlying causes and progression of a disease or condition. Next, researchers design therapies to reverse the condition or stop its progress. Only after these therapies are tested in animals for safety and effectiveness are they then tried in humans. If proven valid, the treatments can be adopted by practicing physicians and dentists for general use among patients.

Basic scientists and clinicians share equal credit in the development of new treatments for acute and chronic pain. Through years of work in laboratories and clinics, inroads into pain relief are made by study, insight, and trial of new therapies.

Several pain treatments now used clinically illustrate how basic research has led to the development of practical measures for relieving pain.

Prostaglandins and Pain

The prostaglandin story dates back to 1930 when scientists reported that fresh human semen causes muscle tissue in the uterus to relax or contract. Later, the active substance responsible was named "prostaglandin" in the belief that it originated in the prostate gland. It was not until thirty years later that researchers realized that prostaglandin arose from the seminal vesicles and was actually composed of a mixture of biologically active compounds. These substances were derived from an acid that is contained in various cell membranes and is released following tissue injury. An intense decade of research then contributed further knowledge about the distribution of prostaglandins, their biological activity, their metabolism, and their role in contributing to the pain and inflammation that follows tissue injury.

Researchers learned that aspirin and other similar drugs could prevent the formation of prostaglandins. Unfortunately, aspirin can have some undesirable side effects; it can interfere with blood clotting and irritate the stomach lining.

The search for a drug more effective than aspirin and not as detrimental led to the introduction of ibuprofen into clinical practice. Ibuprofen (the ingredient in brand name drugs such as Motrin, Advil, and Nuprin) effectively suppressed the pain and inflammation of rheumatoid arthritis. NIDR researchers subsequently showed that ibuprofen was also more effective than acetaminophen in relieving postoperative pain following the removal of impacted wisdom teeth. Furthermore, when ibuprofen was given prior to oral surgery, it was more effective in suppressing postoperative pain than placebo, acetaminophen (Tylenol), or acetaminophen plus codeine.

Researchers at the Pain Research Clinic have also studied flurbiprofen, a drug structurally similar to ibuprofen that is well-tolerated. Flurbiprofen suppresses pain to a greater extent than high doses of acetaminophen or the combination of acetaminophen plus oxycodone (more commonly known as Percocet), generally regarded as one of the most potent combinations used in pain following oral surgery. When flurbiprofen is combined with a long-lasting local anesthetic, many individuals report little or no pain following the removal of impacted wisdom teeth, a procedure that usually produces moderate to severe pain in 90-95 percent of all patients. Fewer side effects have been reported by patients following the flurbiprofen treatment and dentists report that there is no interference with bleeding.

Fifty years of basic and clinical research has led to the development of new drugs for acute pain with a genuine therapeutic advantage. Ibuprofen and flurbiprofen both delay the start and suppress the intensity of postoperative pain to a greater extent than traditional oral analgesic therapy, without an increase in side effects.

New Ways of Administering Opiates

Physicians have long prescribed opiates to successfully treat a variety of pain conditions, even though it was not until ten years ago that scientists discovered how they worked to relieve pain.

Investigators have identified specific sites in the spinal cord and brainstem where morphine and similar opiate compounds inhibit the production of pain signals. In the spinal cord, morphine directly inhibits the cells responsible for receiving and transmitting pain messages from the skin to the brain. In the brainstem, morphine excites the cells which send messages down to the spinal cord to turn off pain-transmitting cells.

A major limitation in the use of morphine and other narcotic pain-relievers, however, is that these drugs also act on many other sites in the brain that cause side effects: nausea, vomiting, sleepiness, unpleasant mood, and depression of breathing. When drugs are taken by mouth, injected into muscle, or injected into the bloodstream, they go to all of these sites in the brain as well as the spinal cord.

A recent innovation in pain treatment is to inject small amounts of morphine-like drugs close to the spinal cord. A high concentration of the drug then turns off pain signals directly at the spinal cord level. Theoretically, since little of the drug reaches the brain which is several feet away, the usual side effects are spared. The drugs are either injected directly into the spinal fluid surrounding the spinal cord (intrathecally) or into the layer of fat that surrounds the sac of spinal cord and fluid (epidurally).

Epidural or intrathecal morphine is often given after surgery. Some doctors are using spinal opiate therapy to treat patients with chronic cancer pain. It is less clear in this group, however, whether the spinal route offers clear advantages over the use of oral opiate pain-relievers. With spinal opiate therapy, cancer patients must either receive repeated injections into a plastic reservoir connected to the spinal space, or must have a pump implanted which can be refilled by injection. This procedure is expensive, entails some risk of infection, and often ceases to be effective when tumors progress.

Most pain specialists agree that intrathecal or epidural delivery of morphine is a good way to provide pain relief, although further research is still needed. Some studies by pharmacologists also suggest that when using spinal opiate therapy, drugs other than morphine may be more effective since morphine has a tendency to quickly reach the brain through spinal fluid.

Tricyclics and Serotonin

The body's pain inhibition system begins in the brainstem, the primitive part of the brain that sends nerve endings to the spinal cord. The pain inhibition system is aided by the release of two neurotransmitters in the spinal cord— serotonin and norepinephrine— that block pain signals originating there.

Serotonin nerve fibers—In this photograph of the dorsal horn, serotonin nerve endings appear as black wavy structures. Serotonin is a neurotransmitter released by nerve endings in the spinal cord. It plays an important role in the body's pain inhibition system by blocking pain signals before they are transferred to the brain.

Treatments that increase the release of serotonin and norepinephrine may be effective pain-relievers. One group of ugs that do this are the tricyclic antidepressant drugs, such as amitriptyline (Elavil) or imipramine (Tofranil). After nerve endings release serotonin, they quickly absorb the serotonin again. Drugs of the tricyclic class block this "reuptake", so that serotonin (or norepinephrine) stays out in the junction between the nerve cells and continues to inhibit the transmission of pain signals.

Although physicians have been using tricyclic drugs for more than 20 years to treat patients with chronic pain, it has not been clear how these drugs actually work. Do tricyclics actually relieve pain themselves? Or, in relieving depression, do they create happier patients who report less pain?

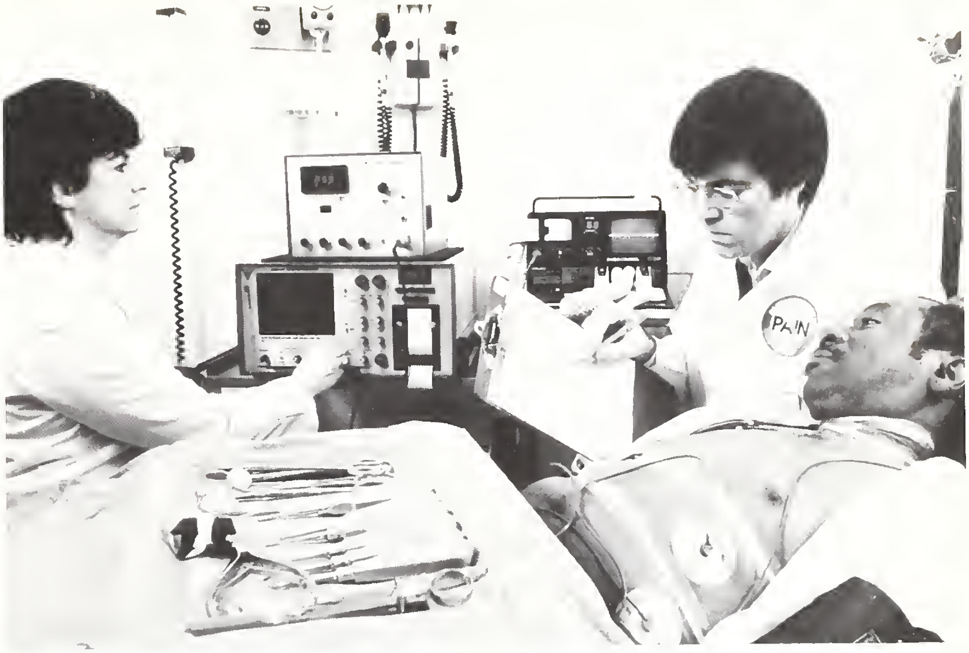
Researchers at the Pain Research Clinic have recently completed a study providing evidence that amitriptyline relieves pain caused by diabetic neuropathy. Patients who were not depressed derived as much or more relief than depressed patients. These findings verify clinical observations that amitriptyline does have a specific pain-relieving effect. Similar results have been obtained by researchers using amitriptyline to treat individuals with post-herpetic neuralgia hingles).■

Pain and Anxiety Control n Dentistry

Pain and dentistry are synonymous in the minds of many people. This is not surprising in view of the discomfort that sometimes accompanies dental procedures. Many people avoid or postpone treatment for this reason, thereby assuring future discomfort as dental neglect can lead to cavities and gum disease. In fact, some 35 million Americans avoid needed dental treatment until forced into the dentist's office with a toothache.

Recognition of the significance of pain and apprehension as impediments to dental care has led to the development of an array of techniques to overcome these obstacles. The techniques include psychological approaches, local anesthetics, and various types and combinations of sedatives and general anesthetic agents. Use of these techniques helps overly fearful individuals who avoid or postpone dental treatment, as well as normal people undergoing stressful dental procedures.

Even individuals who receive routine dental treatment sometimes require pain control to reduce the discomfort associated with fillings or surgical procedures such as tooth extractions and the resulting postoperative pain. General anesthetics or anxiety-reducing drugs are often required during the removal of third molars (wisdom teeth), for example, so that patients can easily tolerate the procedure. The result is that practicing dentists need to be experts in controlling acute pain and anxiety so they can provide successful treatment.



Peggy Wirdzek, R.N. (l.), and Raymond Dionne, D.D.S., Ph.D. (r.), measure a patient's physiological and psychological responses to an intravenous sedative drug given prior to oral surgery. Researchers at the Pain Research Clinic study the use of various drugs to determine which are the most safe and effective in relieving pain and anxiety.

Over the years, dental investigators have been dedicated to improving the treatment of acute pain. During the 19th century, dentists led the pioneers who developed the gases used in general anesthesia. They were also among the first practitioners to adopt local anesthetic agents following their development a century ago.

While the use of drugs has always been associated with some degree of risk, an NIH Consensus Development Conference on "Anesthesia and Sedation in the Dental Office", convened in April 1985, concluded that the use of sedative and anesthetic drugs in the dental office by appropriately trained professionals has a remarkable record of safety.

The panel of experts defined sedation as a depressed level of consciousness, ranging from light to deep, whose main purpose is to control anxiety. Local anesthetics are given along with sedatives to control pain. General anesthesia is a state in which the patient is unconscious and, therefore, relieved of both pain and anxiety. There is some indication that treatment with local anesthesia and conscious sedation carries less risk than treatment with deep sedation or general anesthesia. The risks may increase in the medically compromised, the elderly, and the very young.

Ultimately, however, the decision about which drug or drugs to use in a particular situation rests on the clinical judgment of the dentist. Factors to be considered include the nature, severity, and duration of the procedure; the age, physical, and psychological status of the patient; the individual's level of fear and anxiety; and the patient's previous response to pain control procedures.

The following recommendations were made at the Consensus Development Conference:

- Dental offices should be equipped to handle any emergencies resulting from the use of drugs.
- When conscious sedation, deep sedation, or general anesthesia are used, patients must be monitored for heart rate, blood pressure, respiratory rate, and responsiveness.
- When using deep sedation or anesthesia, at least three individuals, each appropriately trained, are required. One is the dentist; the second is a person whose responsibilities are observation and monitoring of the patient; and the third is a person who assists the operating dentist. Conscious sedation requires two people—the dentist or other licensed professional and an assistant trained to monitor patients.
- Basic science courses and clinical experience in the use of conscious sedation techniques should be taught to the level of clinical competence. Training for deep sedation and general anesthesia requires a minimum of one year advanced study.

- Comprehensive research is needed on morbidity and mortality rates; drug effectiveness studies; monitoring of patients; behavioral and other nonpharmacologic approaches; environmental risk assessment; new drugs; and assessment of whether there are adequate personnel to implement comprehensive teaching and research programs.

Research on dental anxiety has also yielded valuable information. Investigators have found that developing a positive attitude in young children towards dental appointments lays the groundwork for a lifetime interest in good oral health. To prevent dental anxiety from starting, dentists urge parents to bring their children in for dental appointments at a very young age—two and a half to three years old. At this time, the dentist familiarizes the child with the dental chair and equipment and encourages the parents to help their child use preventive measures which will minimize or prevent dental problems.

Researchers are also experimenting with a number of different techniques to reduce dental anxiety in children if it occurs. For example, children may be taught how to manage stress through such methods as controlled breathing and visualizing pleasant scenes. Or they may be given earphones so that they can listen to stories being read while they are quiet and cooperative during their dental appointment. Other studies show that in older children, observing a peer model undergoing dental treatment may help reduce anxiety.

Researchers suggest the following pointers to ease children's fears about dental appointments:

- Teach children good oral hygiene and emphasize that the dentist helps them keep their teeth healthy.
- Never threaten a child with a visit to the dentist.
- Do not prepare a child too far in advance of a dental appointment. A child under the age of five or six can usually be told the same day.
- Put the dental treatment into perspective. If there is going to be pain, let the child know that the pain only lasts a minute or two.
- Select a dentist who is experienced in working with children.

Effective use of pharmacologic and behavioral methods of pain control promises relief of the pain and anxiety that some people associate with dental procedures. For children and adults, a trip to the dentist need no longer be a dreaded experience. ■

What We Learn from Wisdom Teeth

Having wisdom teeth taken out is more than just a trivial operation. When performed at the NIDR's Pain Research Clinic, this relatively simple surgical procedure yields a wealth of information about the effects of surgery on the body. Scientists use the extraction of wisdom teeth as a model for acute pain because it is applicable to the acute pain that results from surgery in other parts of the body.

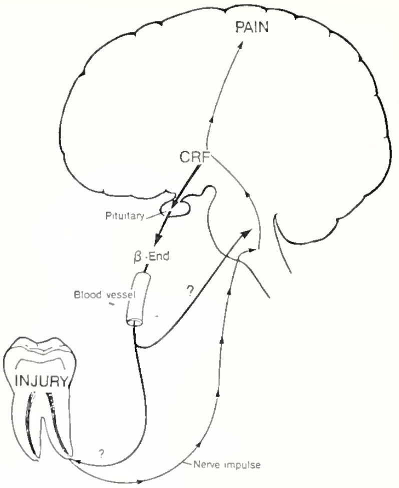
People undergoing wisdom teeth removal are ideal for study. Typically, they are normal, healthy patients. Prior to surgery—the removal of teeth—these people are a near perfect model of patient anxiety. During the procedure, researchers can measure how the stress and pain caused by the surgery affects patients. Postoperatively, these individuals can be given various drugs to determine which agents are most effective in reducing pain.

Researchers at the Pain Research Clinic are especially interested in hormonal changes that occur in the body in response to surgical stress. Many hormonal changes are governed by the pituitary gland, located in the base of the brain. This gland is often referred to as the body's master gland because it regulates such functions as growth, reproduction, and metabolism. The pituitary also has another critical function—it controls the body's ability to adapt to stress.

When the body encounters stress, from surgery for example, the pituitary gland secretes the hormone adrenocorticotropin (ACTH). ACTH in turn stimulates the release of steroids such as cortisol that regulate our immune and metabolic responses to stress. People who are unable to secrete these hormones cannot survive stressful situations. Addison's syndrome is the name of such a disorder. Even a surgical procedure as minor as the extraction of wisdom teeth could prove fatal for individuals who suffer from Addison's syndrome.

While the pituitary gland secretes ACTH, it also releases another hormone in response to stress, called beta-endorphin (B-End). Beta-endorphins were recently discovered in 1975. Scientists know that the hormone is 20-100 times stronger than morphine in relieving pain. They also know that the hormone is secreted directly into the bloodstream and circulates throughout the entire body. But researchers still need to learn what the functions of beta-endorphins are in relation to stress and pain.

To answer these questions, scientists at the Pain Research Clinic study the release of beta-endorphins in individuals undergoing wisdom teeth removal. During the actual surgery, these patients experience dramatic increases in their levels of beta-endorphins. The levels decrease following surgery and increase once again during the onset of postoperative pain.



Investigators at the NIH Pain Research Clinic study the hormone beta-endorphin (B-End) and its role in pain relief. The process begins with the secretion of Corticotropin Releasing Factor (CRF) by the brain. CRF controls the pituitary gland and stimulates it to secrete beta-endorphins in response to stress. B-End then circulates throughout the bloodstream and may act to relieve pain in several ways: either at the site of injury, or in the brain.

Researchers are looking at the effects of different drugs on the release of beta-endorphins. When patients are given a placebo—in this case a pill "to control stress" during the surgical procedure—their beta-endorphin levels increase. But when they are given valium, a tranquilizer, or fentanyl, a narcotic analgesic, the release of beta-endorphins is actually blocked. These findings suggest that valium removes the patient's anxiety and perception of stress, and less stress leads to less beta-endorphins. Fentanyl, on the other hand, may act directly at the pituitary gland to inhibit the release of beta-endorphins. In addition, like valium, fentanyl also may reduce an individual's perception of stress. Patients given naloxone—a drug that reverses the effects of a narcotic—experience greater pain during surgery and have higher levels of beta-endorphins.

Investigators are also studying Corticotropin Releasing Factor (CRF), a hormone secreted by the brain that controls the pituitary gland. CRF stimulates the pituitary to secrete beta-endorphins. Patients given CRF have greater beta-endorphin levels than patients given placebo. Significantly, patients given CRF also experience less postoperative pain. These studies indicate that pituitary hormones may be critically involved in the postoperative stage, not only in the regulation of metabolism but also in the modification of postoperative pain.

Future studies at the Pain Research Clinic will look at the effect of new classes of drugs on beta-endorphin release and the role of beta-endorphins in modifying pain perception. From these studies scientists will learn more about how the body responds to surgical stress and which drugs provide pain relief without the side effects of narcotics. As new avenues of research in pharmacology and physiology are broached, investigators will have definitive answers about the role of hormones in relieving pain. ■

How We Measure Pain

You are walking barefoot at home, oblivious to all but your own thoughts, when suddenly you stub your big toe on a chair. Pain overtakes the toe. You silently (or loudly) chastise both the chair and yourself. But how would you describe the aching toe that is now the sole focus of your attention? Is the pain throbbing, beating, or pounding? Is it agonizing, tender, or wrenching? And how does this pain compare to pain you have experienced in other instances?

Pain is a difficult thing to describe and measure because each of us perceives it differently. Our moods, emotions, cultural background, and previous experiences influence how we feel and react to pain. What one person believes is the worst ache possible, may to someone else, feel like just slight discomfort. The stubbed toe that is a minor setback to one individual may be totally debilitating to another.

Researchers need to measure pain to learn how intensely individuals are feeling pain and to monitor the effectiveness of treatments. Much of what we know about pain sensation and pain treatment is learned through research studies in which patients report what they feel. While these sensations are subjective, pain can only be defined through personal descriptions of pain experiences.

To help standardize pain assessment, NIDR scientists at the Pain Research Clinic have developed new scales to verbally measure and quantify pain. Patients report separately on two major aspects of pain: its unpleasantness and its intensity. Words such as "weak," "mild," "moderate," and "intense" are used to describe the intensity of pain sensations, while "annoying," "unpleasant," and "distressing" are applied to the unpleasantness component. They are instructed to choose the words which most aptly describe what pain, if any, they are feeling during experimental pain procedures. They receive either electrical stimulation of their teeth, or heat applied to their arm, ranging in temperature from 110° to 124° F. These studies show that the amount of intensity or unpleasantness implied by each word is similar for different patients. Moreover, participants in these studies are able to use these words to accurately rate the intensity or unpleasantness of pain sensations.

Researchers at the Pain Research Clinic also measure the effects of various treatments on pain unpleasantness and intensity because treatments act on pain in different ways. For example, in some situations narcotic analgesics such as morphine reduce the intensity of pain without reducing the unpleasant, emotional component; tranquilizers such as diazepam reduce pain unpleasantness but not pain intensity. The results of a study can be influenced by the type of pain scale used to measure pain. A scale that only measures the effect of a treatment on pain unpleasantness would conclude that narcotics are ineffective in relieving pain. Thus, it is important for researchers to use more than one type of pain measure to avoid missing certain effects or making erroneous conclusions about pain study results.

Much of what scientists know about pain sensation is learned through research studies in which patients rate experimental pain. Electrical stimulation of patients' teeth is one such procedure used to measure patients' responses to pain intensity and unpleasantness. Studies using these methods provide information about the mechanisms of pain and pain control.

New measures of clinical pain have also been developed that assess a patient's ability to describe pain sensations accurately. One method requires patients to rate experimental pain against the pain associated with their own disorder. This method shows that most patients can accurately describe how much pain they feel. It also identifies those who have difficulty doing so.

Although it is now possible to measure pain more accurately in adults, one problem researchers still face is how to perform these measurements in children. When children have cancer, for example, clinicians need to measure their pain to assess how well their pain medications are working. Pediatric descriptors include words and phrases that young children can understand, such as "the biggest pain, the worst possible pain," "it hurts somewhere between a bit and a lot," or "it's a little ouch." For very young children who may not yet have the verbal skills required to use these scales, illustrations are often used rather than words. A range of faces, from happy to sad, is used to represent a range of pain. Children are asked to select the face that reflects how they are feeling. Other scales use a thermometer, and children are asked to mark where on the thermometer their pain registers—on the high end, the low end, or somewhere in between. Another method offers childen the chance

Dr. Richard Gracely (r.), a psychologist at the Pain Research Clinic, applies thermal stimulation to a patient's arm in a study of pain perception. The patient selects words from a monitor to describe the pain sensations she feels.

Christopher, a cancer patient, squeezes "Oliver the Octopus" to indicate how much pain he feels. A pressure-sensing device is concealed inside the octopus. The strength of Christopher's squeeze registers on the numbered dial held by Judy Dothage, R.N. Researchers at the NIH Pain Research Clinic are testing this method to see if it is a valid way of measuring pain in children.

to squeeze a blood pressure bulb that has a puppet sitting on top. The pressure of their squeeze indicates their level of pain.

The results of the Pain Research Clinic's studies demonstrate that the significant dimensions of pain can be accurately measured by both verbal and nonverbal methods. As pain measurement scales provide important information about pain treatments, researchers can simplify the complexities of a phenomenon as subjective as pain and help in the development of new agents and techniques to block pain. ■

Dr. Elyse Singer, a neurologist at the Pain Research Clinic, examines the muscles of a patient suffering from chronic tension headaches. Headaches afflict seventy million people in the United States, and many of these are chronic tension headaches.

Current Chronic Pain Studies at NIH

Investigators at the Pain Research Clinic study chronic pain to advance our knowledge about pain mechanisms, measurement, and relief. They study chronic pain conditions that afflict large numbers of people in the United States. Moreover, these are conditions for which there is an organic basis for pain, where pain is localized to known sites, and the pain is similar among patients.

Those conditions currently under investigation at the Pain Research Clinic include:

- Diabetic Neuropathy—Previous studies showed that amitriptyline relieves pain caused by diabetic neuropathy, but also causes many side effects. Fluoxetine is a new antidepressant drug that works in the same way as amitriptyline without causing adverse reactions. Patients in this study receive fluoxetine for eight weeks and a placebo for eight weeks. If fluoxetine is shown to provide pain relief, it will be made available to individuals with diabetic neuropathy who are unable to tolerate the side affects of amitriptyline.
- Post-Herpetic Neuralgia—After an attack of shingles, pain sometimes persists for months or even years. Little is known about how to eliminate this pain. At the Pain Research Clinic, individuals with post-herpetic neuralgia, who are otherwise in good health and mind, receive amitriptyline, lorazepam, and a placebo to determine if any of these families of drugs are effective pain relievers. Future studies will use new drugs from that family shown to provide the most pain relief.
- Orofacial Pain—Individuals with facial pain of muscular origin receive either ibuprofen, diazepam, an ibuprofen-diazepam combination, or a placebo for a one-month period. The purpose of the study is to determine the effectiveness of medications on a short-term basis in treating the myofascial pain dysfunction syndrome.
- Myogenic (Tension) Headache—This is a long-term study in which individuals who suffer from chronic tension headaches receive either drugs to control pain, placebo, or non-pharmacological treatment such as physical therapy. The study also assesses new methods of quantifying muscle pain, tenderness, and spasm using mechanical devices which measure muscle tenderness and range of motion.
- Low Back Pain—The effects of deep brain electrical stimulation for treating intractable chronic back pain are being examined. This controversial technique, which requires brain surgery, is being used in patients at the University of California at Los Angeles whose low back pain has been unsuccessfully treated by other methods. The stimulator technique is believed to activate the brain's pain-suppressing mechanisms, thereby reducing pain. These patients are then evaluated at the Pain Research Clinic for independent testing of the procedure's effectiveness.
- Cancer—Investigators are evaluating the effectiveness of new drugs in relieving pain in cancer patients.

Many cancer patients also experience painful side effects as a result of their medical treatment. Chemotherapy, for example, can cause oral mucositis—inflammation of the soft tissues of the mouth. To relieve the pain associated with oral mucositis, investigators are exploring the use of the drug fentanyl which is applied and absorbed through a skin patch. Other studies are also looking into the use of mouthwashes—including a motrin elixir—to relieve oral mucositis pain.

Investigations of cancer pain also include studies of phantom limb pain in adults and children, and studies of the causes and treatment of cancer pain in children.

Individuals who participate in studies at the Pain Research Clinic are critical to the success of NIH's pain research program. Not only do they benefit from new and improved methods of pain control, but they also help set standards for pain treatment nationwide. ■

Pain Management Today

While the field of pain management is relatively new, many treatments available today are rooted in therapies several thousand years old. The goals of modern pain therapy are twofold: to apply appropriate treatments based on the patient's type of pain problem and needs; and to expand upon the kinds of pain treatments available.

Pain problems fall into three generally well-accepted categories: acute pain, cancer pain, and chronic pain. Clinicians approach each with a different strategy.

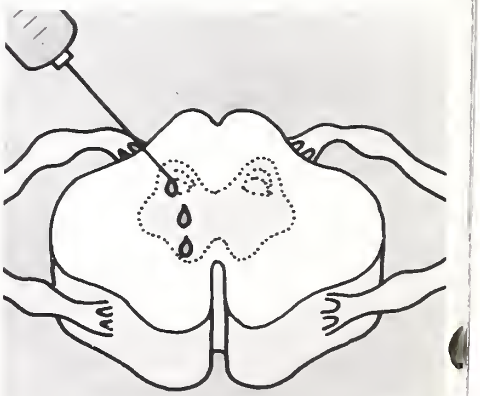
Acute Pain

Acute pain is of recent onset and limited duration, and usually has a known cause such as surgery. Many individuals with acute pain suffer from anxiety, wondering when and if their pain will end.

Adequate doses of analgesics such as narcotics, taken on a round-the-clock basis, usually relieve acute pain. The steady influx of drugs avoids the "peaks and valleys" of severe pain and the dangers of oversedation, and helps overcome the sense of anxiety generated by the fear of inadequate or irregular pain relief.

Several methods are used to enhance the effectiveness of narcotic analgesics, including:

- Patient-controlled analgesia—narcotics administered intravenously by a mechanical pump. The patient controls the rate of administration, with safeguards built in to prevent overdose.
- Epidural analgesia—narcotics are administered around the spinal cord through an epidural catheter that is placed before surgery and removed several days later.
- Drug combinations—opiate drugs combined with nonsteroidal anti-inflammatory agents such as ibuprofen or aspirin provide enhanced pain relief.


Epidural anesthesia, in which narcotics are administered around the spinal cord, can provide relief for acute pain.

- Prolonged regional (local) anesthesia—provided by creating a nerve block. A catheter is inserted eoperatively and left in place for sev-al days during the postoperative period. An anesthesiologist then periodically injects anesthetic solution into the catheter.
- Transcutaneous electric nerve stimulation (TENS) may reduce acute pain, particularly in patients who have suffered musculoskeletal injury. TENS is a device that delivers low-intensity electric current through the skin to the nerves and can reduce the amount of narcotics required postoperatively.
- Psychological techniques prepare patients to cope with pain and anxiety. nformation about procedures and postoperative sensations can be presented in various ways including educational mate-ials or by introducing patients to others who have successfully undergone the same procedure. Hypnosis and progressive muscular relaxation can also be aught prior to surgery to enhance patient control over pain and stress.

Cancer Pain

Pain control for the terminally ill has been greatly aided by the hospice movenent which emphasizes the relief of suf-ering. The mainstay of cancer pain ther-y is to provide adequate doses of arcotic analgesics on a regular schedile. New delivery systems have been de-eloped that improve the effectiveness of ıvailable narcotic agents. These systems nclude:

- Long-acting, time-release oral prepa-ations, and rectal and sublingual (under he tongue) preparations for patients who annot take oral medications.
- Transdermal narcotic administra-on—A stick-on patch saturated with a arcotic, such as fentanyl, slowly re-eases medication into the skin over a pe-od of days. The dosage can be in-reased by adding more patches. ransdermal fentanyl is under investiga-on and has not yet been released for videspread use.
- Pump devices—Permanently im-lanted pump devices continuously re-ease narcotics into the blood or nervous ystem.

lon-pharmacologic techniques include:

- Neurolytic nerve blocks—Specially ained anesthesiologists inject solutions nto the peripheral nerves or spinal cord destroy the nerves that carry pain nessages to the brain. This procedure rries the risk of serious neurological mage and is reserved for patients who ave a limited life expectancy. To be eli-ible, patients must previously have re-ponded to temporary blocks with local nesthesia but failed to respond to con-entional pharmacologic methods.

Nurses play an important role in the Pain Research Clinic's multidisciplinary approach to pain management. When joining a pain study, patients see a doctor, social worker, psychiatrist, and nurse during their initial visit to the pain clinic. Nurses assess each patient's health by checking blood pressure; determining if there are any drug allergies; finding out what medications have been used in the past; and learning about sleep habits, alcohol intake, activity level, and social and family life. Nurses also pinpoint when patients need to be taught coping strategies to better handle their pain syndromes, and they help design individualized pain management techniques for patients. A patient suffering from diabetic neuropathy, for example, may need to learn about proper foot care.

During the course of pain treatment studies conducted by the Pain Research Clinic, nurses monitor patients for any side effects that may result from drugs used in the study. Nurses call patients at home several times a week and adjust their medication as needed. This constant contact enables Pain Research Clinic staff to assess the progress of patients in between their scheduled visits to the pain clinic.

- Neurosurgical procedures—Procedures such as anterolateral cordotomy, in which portions of nerves in the spinal cord are severed, can alleviate otherwise intractable pain. This type of procedure is most helpful in patients who have leg pain on one side of their bodies.

Chronic Benign Pain

Pain that is not caused by a malignancy and that has lasted longer than six months falls under the category of chronic "benign" pain. Low back pain, headache, orofacial pain, diabetic neuropathy, and arthritis are among the conditions that may become chronic. Some patients may not have a definitive diagnosis. Chronic pain interferes with every aspect of living and is associated with depression, sleep disorders, loss of employment and social contacts, and disruption of family relationships. Patients cannot expect the pain to stop, which complicates their lives further. Some individuals may misuse analgesic and sedative-hypnotic drugs in a fruitless attempt to gain relief; but narcotics and minor tranquilizers are rarely the best way to treat long-term chronic pain. These agents lose their effectiveness over time and may contribute to depression.

The most important development in the treatment of this type of pain is the growth of pain treatment centers staffed by a variety of health care professionals. Multidisciplinary pain treatment centers are located in every region of the United States. The staff at these centers specializes in the treatment of pain and offers both physical and psychosocial assessment of the patient. When pain cannot be cured, it can at least be reduced or managed so that patients can lead functional lives.

Goals in the management of chronic pain are to:

1. Reduce or eliminate as many medications as possible, particularly those that can cause addiction, depression, or toxicity.
2. Reduce "pain behaviors" that disrupt normal living.
3. Increase physical and social activity. This includes a return to employment whenever possible.

Methods used to manage chronic pain include:

- Detoxification—Patients accustomed to taking large doses of narcotics or sedative-hypnotics can be placed on a simplified regimen of long-acting preparations such as methadone. The dose of medication is slowly reduced as other methods of pain therapy are gradually introduced.
- Use of non-addictive medications—Nonsteroidal anti-inflammatory drugs or tricyclic antidepressants can provide good analgesia for some pain syndromes. Tricyclic drugs improve mood and sleep and are particularly helpful in relieving pain caused by migraine, tension headache, and neuropathies.
- Use of antiepileptic medications—Drugs such as carbamazepine (Tegretol) and phenytoin (Dilantin) are helpful in relieving pain in a limited number of specific pain syndromes, such as trigeminal neuralgia, also known as "tic douloureux."
- Surgery—Although most chronic nerve pains do not respond to surgery, many patients with trigeminal neuralgia not controlled by medication have gained relief from surgical procedures. One such procedure is "radiofrequency rhizolysis," in which a long needle is placed through the cheek through a tiny opening in the skull and a weak electrical current is

used to selectively destroy a very small number of nerve fibers. Another procedure is called "microvascular decompression." The skull is opened and a protective material is placed between the trigeminal nerve root and any blood vessels which might be irritating the root. Complete destruction of the nerve is to be avoided as a treatment since it leads to loss of sensation, especially of the eye, and rarely provides more than a year or two of relief.

- TENS and acupuncture—TENS may be helpful in relieving chronic musculoskeletal pain. The TENS device can be worn by the patient and turned on and off as needed. Both traditional (manual) acupuncture and electrically augmented acupuncture are also used in some pain clinics. TENS and acupuncture are not effective in every individual and only a trial experience will tell who will benefit.
- Nerve blocks—While useful in relieving acute pain, nerve blocks are of limited use in the treatment of chronic pain. Local nerve blocks can produce short-term pain relief, however, by temporarily stopping the transmission of pain signals.

Permanent nerve blocks, such as neurolytic blocks, frequently fail to relieve chronic pain syndromes and pain often recurs within a year's time. The solutions that are injected into a patient's nerve actually destroy part of the "messenger system." This usually leaves the patient numb in that area. However, pain may return if the pain pathway reestablishes itself or if the damaged stump of nerve begins to transmit its own pain signals.

A better use for nerve blocks is in the treatment of a relatively uncommon pain syndrome called "reflex sympathetic dystrophy" or "causalgia." Individuals with this syndrome experience burning pain in their extremities and may even develop loss of function of their extremities and atrophy of bone and soft tissues. The syndrome is caused by a dysfunction in one of the body's nervous systems—the sympathetic nervous system—responsible for controlling blood flow in the extremities. When local anesthetics are injected into the ganglia—a mass of nerve cells outside the spinal cord—long-term pain relief can be achieved. In some cases curing the syndrome is possible. Guanethidine, a drug used for the treatment of severe hypertension, is also effective in the treatment of reflex sympathetic dystrophy. The drug is injected directly into the affected extremity rather than the ganglia. At this time, however, guanethidine is not readily available in the United States.

Trigger point injections may be useful in reducing referred pain and spasm so that patients can participate in a successful exercise program. A dilute solution of procaine is injected directly into tender, painful muscles.

- Physical therapy—is of prime importance in the treatment of many pain syndromes. Physical therapy can: identify biomechanical factors that cause or perpetuate pain; stretch and strengthen muscles and restore range of motion; gradually reintroduce the patient to physical activity; and educate patients about correct posture and body mechanics to prevent reinjury.
- Psychological techniques—Psychological techniques are often used to improve outcomes in the treatment of chronic pain. These techniques include hypnosis to promote dissociation from pain; biofeedback and relaxation techniques to reduce spasm; coping skills to help deal with pain and anxiety; and identification and reduction of "pain behaviors" and substitution of "well behaviors" through a program of behavior modification. Whenever possible, the patient's family and friends should be included in this aspect of rehabilitation.

By applying knowledge from basic and clinical research, pain treatment centers throughout the country have begun to make chronic pain therapy more effective. Individuals who would like to avoid a lifetime of narcotics and barbituates or repeated surgery can seek assessment for alternative methods of treatment. New discoveries in the neurochemistry of pain, the development of safe and more specific drugs, the increased use of new methods of pain treatment, and most importantly, improved professional education and awareness promise to increase the quality of life for people suffering from chronic pain. ■

Future Directions in Pain Research and Therapy

Narcotics, anesthetics, aspirin-like drugs, and surgical severing of pain pathways have been the traditional mainstays of pain management. With the emergence of new knowledge about the initiation, transmission, and perception of pain, scientists are working on innovative therapies aimed at selectively blocking key steps in the pain process.

Future advancements in the relief of acute and chronic pain will most likely come from two major areas: the development of agents that alter the transmission of neurochemicals in pain pathways; and the development of natural methods of activating the brain's own pain-suppressing systems. Within the brain the naturally-occurring opiates interact with receptor sites involved in the suppression of pain signals. Narcotic analgesics, such as morphine, also act at these receptor sites. Intensive research is underway to identify receptor subtypes which result in analgesia without producing the undesirable side effects of narcotic analgesics such as respiratory depression and drug dependence.

Stress, acupuncture, and placebo can produce a reduction in pain related to the activation of opiate pain-suppressing systems. Hypnosis and some forms of placebo treatment activate other pain-suppressing pathways not involving opiates. Current research is attempting to define the structure and function of the different types of pain-suppressing pathways. Research is also identifying behavioral interventions which influence pain perception and pain-related behaviors, such as inactivity. When behavioral approaches to pain reduction are effective, they have the additional advantage of avoiding potential adverse effects sometimes associated with pharmacological and surgical methods of pain control.

The search also continues for chemical agents that initiate nerve activity in the periphery—the skin, muscle, and internal organs of the body—in response to painful stimulation. Bradykinin, prostaglandins, histamine, and other polypeptides have been suggested as the possible chemical agents. These substances occur naturally and are found in higher concentrations after tissue injury. However, their specific roles in transmitting pain signals are not known. Such knowledge could lead to new agents that block pain in the periphery without suppressing normal sensations or causing adverse effects in the central nervous system such as those produced by narcotics. Non-steroidal anti-inflammatory agents, for example, which block the release of prostaglandins in the periphery, have caused fewer side effects and been proven more effective in relieving acute dental pain than mild narcotic-analgesic combinations.

The motivational, cognitive and attitudinal dimensions of pain are other promising new areas of brain research. Using animals trained to perform behavioral tasks related to these aspects of pain,

Group meetings at the Pain Research Clinic are a time for staff neuroscientists, neurologists, oncologists, dentists, pharmacologists, psychologists, and nurses to discuss each patient, collaborative pain studies, and pain mechanisms.

scientists can now study behaviors and brain nerve cell activity simultaneously. A better understanding of pain mechanisms may lead to the design and testing of more specific and more effective pain control methods.

Dramatic advances in the study of chronic pain will occur as understanding of the complexity of persistent pain increases. Improvements in diagnostic procedures, appreciation of the importance of psychological factors in chronic pain, controlled studies of new drugs, and a multidisciplinary approach to chronic pain are leading to a clearer definition of pain syndromes and specific therapies.

Future improvements in patient care will depend on improved patient education, incorporation of research findings with clinical innovations, and dissemination of this new information. As the public is better informed about health issues, they should be skeptical about receiving therapies that are not well validated or are unnecessarily hazardous to the patient. In dentistry, for example, conscious sedative techniques have replaced routine general anesthesia for surgical procedures out of mutual recognition by clinicians and the public that it is usually safer to work on a sedated but awake patient.

Likewise, the futility of surgical procedures to control most chronic pain conditions should lead clinicians and patients alike to exhaust all other pain control methods prior to using such an irreversible procedure. Patients are entitled to pain therapies that are conservative, safe, and effective. Such methods to relieve acute and chronic pain are on the horizon. With new strides in the understanding of pain and the development of innovative pain control methods, more individuals will be able to lead normal, fulfilling, and most importantly, pain-free lives. ■

PATIENT REFERRAL
TO NIH PAIN RESEARCH CLINIC STUDIES

The NIH Pain Research Clinic is currently accepting qualified patients for research studies on the extraction of third molars (wisdom teeth), chronic facial pain, diabetic neuropathy, post-herpetic neuralgia (shingles), and tension headache.

If you would like to participate in any of these research studies, have your dentist or physician complete the form at the bottom of this page or send a letter of referral to the Clinic.

At this time, the NIH Pain Research Clinic is recruiting only for the above-mentioned studies. The Clinic does not provide treatment except during the course of research studies.

PATIENT REFERRAL
TO NIH PAIN RESEARCH CLINIC STUDIES

PATIENT NAME: ______________________________

PATIENT ADDRESS: ______________________________

HOME PHONE: ____________ **WORK PHONE:** ____________

WHAT PATIENT IS BEING REFERRED FOR:

_____ Third Molar Removal
_____ Diabetic Neuropathy
_____ Tension Headache
_____ Chronic Facial Pain
_____ Post-Herpetic Neuralgia

SIGNIFICANT MEDICAL HISTORY:

REFERRED BY: ______________________________

ADDRESS: ______________________________

OFFICE PHONE: ( ) ____________

SIGNATURE ____________________ DATE ____________

MAIL TO: NIH PAIN RESEARCH CLINIC
Building 10, Room 3C403
National Institute of Dental Research
National Institutes of Health
Bethesda, MD 20892

PHONE REFERRALS: (301) 496-0394

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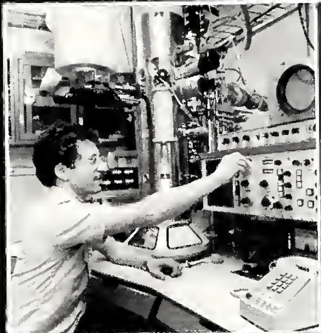

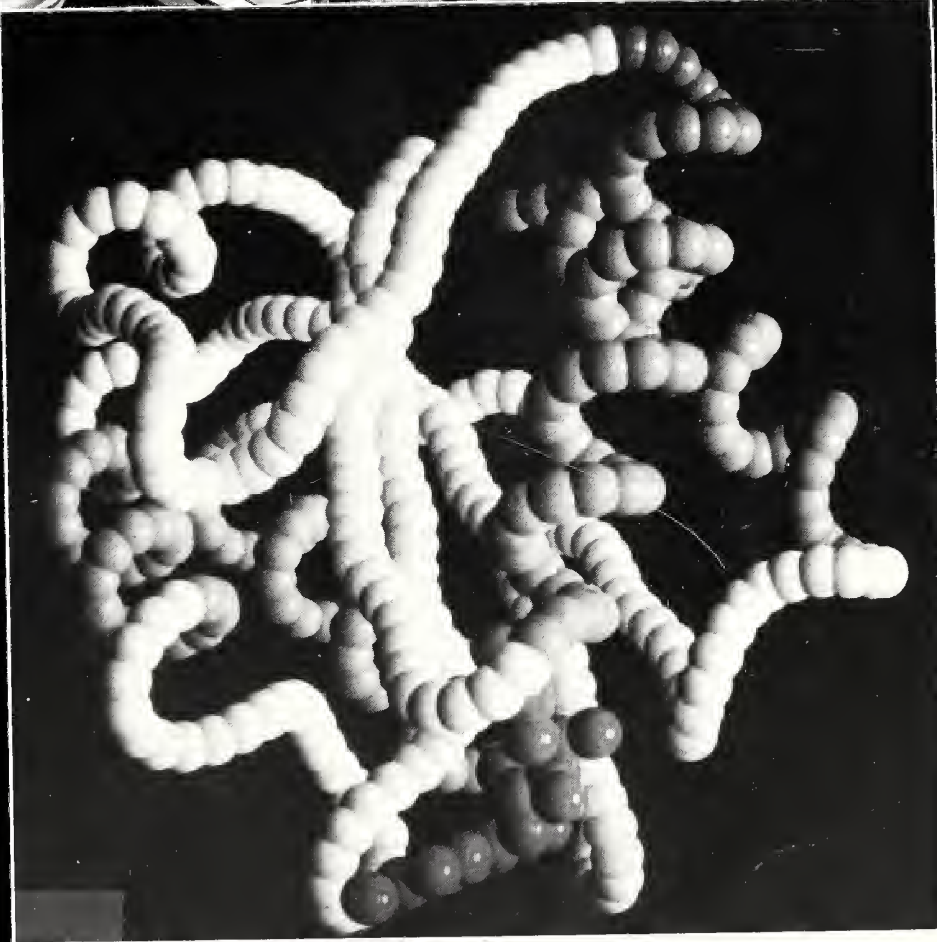

Special Issue:
Computers in Biomedical Research

Introduction

For more than two decades, the NIH approach to computing has grown and adapted to continuing challenge in both biomedical research and computer technology. Today, molecular biology is at the forefront of scientific enterprise. The ability of computers to transform complex numerical descriptions of large biological molecules into dynamic three-dimensional images allows scientists to see and explore interactively the structure of specific molecules at a level unparalleled in science before. In addition, computers are used to model graphically viruses, membranes, and other subcellular structures in order to more fully understand how structure relates to function in health and disease.

At NIH's Division of Computer Research and Technology (DCRT), scientists are developing and using computer technology to solve some of biomedicine's most complex physical and chemical problems. The challenge facing the DCRT is to maintain the intellectual linkage between science and computers in the scientific workplace, thus bringing new horizons to the world of biomedical research.

Acknowledgements

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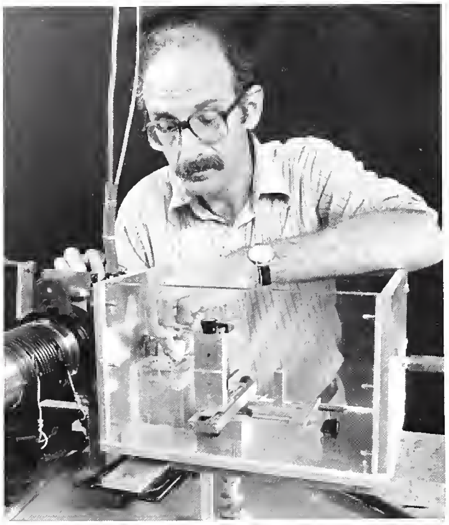
Scientists from across the nation and around the world make use of NIH's powerful computer system for modeling molecules. The system allows scientists to see what large molecules—such as proteins, enzymes, and antibodies—look like in three dimensions. Knowing how its parts are assembled and how a molecule reacts with other molecules helps scientists understand its function in health or disease.

See page **2.**



Computer technology offers the physical scientist new ways to examine biological processes.

To understand cell biology, scientists must understand the nature of physical forces that allow biological molecules to find each other and fit inside cells.

Computers are needed to analyze these forces that ultimately lead to molecular assembly.

See page **5.**

Information from images has innumerable applications in science and medicine.

At NIH, biomedical scientists employ image analysis for a wide variety of research goals.

During 1980, DCRT in collaboration with other users and potential users, designed a general purpose computer facility to aid the acquisition, display, and analysis of images such as electron micrographs, CAT scans, and radiographs. Since its installation in 1983, hundreds of NIH scientists have been using this system.

Sophisticated computer hardware and software techniques enable researchers to extract new information from biological and biomedical images. NIH's state-of-the-art image processing facility exposes new horizons in the biomedical world.

See page **8.**

Networking—the linking of computer equipment and computer users to one another—is attracting interest among the scientific community. Local Area Networks are an efficient way for offices, laboratories, and computer facilities to share equipment and resources. Collaboration via computer between scientists at remote locations is becoming more and more common as technology allows them to exchange ideas and information more easily.

See page **12.**

Computer Graphics: The Art and Science of Reproducing Nature

Marlene Stein Schooler and
Joan Hartman Moore

Can man actually beat nature at its own game? Several scientists, especially molecular engineers, think so and with the use of revolutionary computer graphics they are discovering how to create "instant evolution" to alter and conceivably improve protein design.

The computer graphics revolution is a significant development of genetic engineering, allowing scientists to compile and compare substantial amounts of data on the structure of proteins and other biological building blocks. In addition, computer graphics—the methods and techniques used to construct data to or from graphic display on computers—have transformed scientists' ability to envision the shape of molecules and to predict the effect of their alterations. This capability is vital because a protein's shape determines its function.

NIH's Division of Computer Research and Technology (DCRT) houses a computer graphics system that produces molecular graphics. Developed nearly 9 years ago by computer graphics specialist Richard J. Feldmann and his former colleague Thomas Porter, it is now one of the most powerful molecular graphics systems in the world.

The system allows scientists to inspect in three dimensions the contours and textures of complex biological molecules such as proteins, atoms, and nucleic acids. The image of the molecule can be turned around, enlarged, reduced, or highlighted, allowing the scientist to view the molecule from any angle, in its entirety, or in detail. The molecule also can be videotaped or photographed for later study.

Understanding how large molecules such as enzymes, antibodies, or other proteins function in health or disease depends on understanding how their various properties are assembled and how the whole molecule reacts with other molecules. The DCRT molecular modeling system enables the scientist to figuratively "hold" a molecule and examine it from the outside and inside.

Once a protein's design is determined, scientists can predict how that design may be improved. Molecular graphics enable the effects of these changes to be discovered almost immediately. Studies of structures such as sodium channel, adenovirus, and DNA have been aided substantially with the DCRT molecular graphics system.

Before Feldmann and Porter developed the DCRT system, scientists used three-dimensional line drawings, produced by an earlier computer system, and hand-constructed wire models. But these models were expensive and construction took weeks of a scientist's time. According to Feldmann, the line drawings and wire models showed only the protein's skeleton.

"Proteins are like people," he explained. "They're flesh and bones. It's really the surfaces of the protein that count, because it is through them that the protein interacts with its environment. The skeleton gives you some understanding of the protein, but it doesn't really tell you how it functions in biological systems."

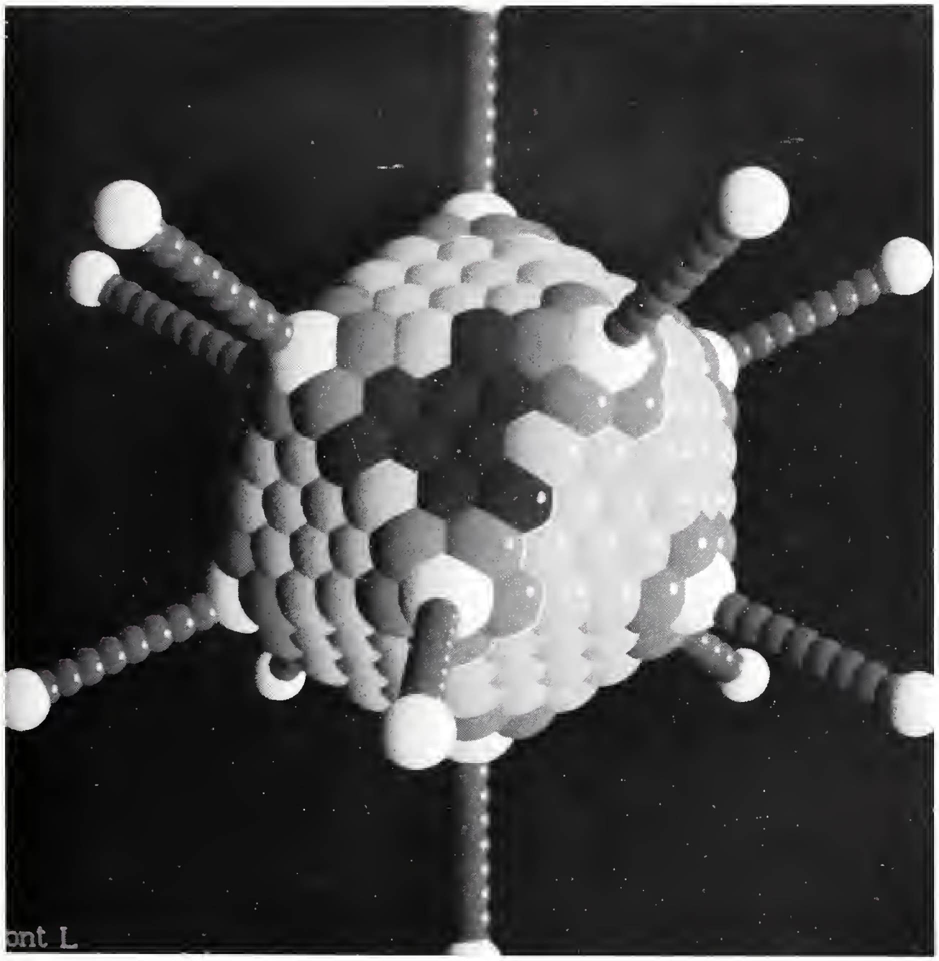
Although protein design is a new, largely unexplored field, its results to date are encouraging. E.T. Kaiser, a protein chemist at Rockefeller University and his coworkers, completely designed calcitonin, a naturally occurring hormone that regulates calcium levels in the blood and ensures bone strength. Kaiser and his associates used computers to model the molecule's structure, attempting to create something vastly different yet functional.

Molecular and Cellular Graphics Workstation
A molecule's shape determines its function. Scientists who know the design of a molecule can then predict how that design might be improved. The effects of such changes can be seen rapidly with computers.
When NIH scientists need to study molecules, they turn to DCRT. There, pioneers in computer graphics, such as Richard Feldmann, have worked for two decades to create what is now one of the most powerful computer graphics systems in the world.
DCRT computer specialists create three-dimensional computer models of structures such as atoms and proteins. Using the computer as a tool has aided the study of sodium, DNA, adenovirus, and many other structures. NIH PHOTO 2134

Although the artificial calcitonin hormone seems to work as well as the natural one, two-thirds of its chemical composition is different. Through redesigning, the man-made protein could prove superior to the natural protein at treating bone disorders.

David and Jan Richardson, protein engineers at Duke University in North Carolina, are involved in designing new molecular structures. With the use of detailed, computer-generated protein design principles, they make up proteins, decide on their shape, then design them. The Richardsons, like others involved in protein engineering, are not concerned at this point with potential uses for their creations. Instead, they are trying to determine how nature designs proteins and molecules that create structure inside living cells. Ultimately, their goal is to understand the design of life's chemicals and to alter them successfully at will.

For nearly 2 decades, NIH scientists have been improving techniques to shorten the time required to construct molecules. The new, advanced molecular graphics facility uses an array processor that is 150 times as powerful as the laboratory computer of the last generation enabling this work to be accomplished overnight.



Adenovirus Model
This is an adenovirus modeled from electron micrograph data on the DCRT Molecular and Cellular Graphics Workstation.
Adenovirus is one of a group of viruses found in all parts of the world, causing disease of the upper respiratory tract and eyelid. NIH PHOTO 2135

An array processor is a device used with a minicomputer that reduces by several orders of magnitude the time required to perform strings of iterative arithmetic. This greatly speeds up scientific computing, with its complex mathematical problems.

Very few computer graphics systems worldwide are comparable to the DCRT system for drawing space-filling images that show the surfaces of molecules. The system initially was used only by NIH scientists, but its superior capabilities quickly became known and crystallographers, pharmacists, and biochemists from all over the world now use it regularly.

Crystallographers in the Molecular Structure Section, Laboratory of Molecular Biology (LMB), at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), routinely use their molecular graphics in research on biological molecular structures. The line drawing system is used to determine the molecular structures, and the space-filling system helps to present the results.

According to Dr. Richard Bott, formerly a crystallographer in LMB and now at Genentech in South San Francisco, one of the most important points in studying proteins is figuring out how they work, and the answer is in the geometry.

"With biological molecules such as proteins, which contain thousands of atoms, it is difficult to demonstrate what is what within the molecule," Bott said. "You can do this quite clearly with molecular graphics by using color to highlight various parts of the molecule."

Protein chemists, such as Kaiser and the Richardsons, are attempting to create proteins that are more reliable, more active, or more beneficial than the ones nature provides through evolution. But they are just beginning to understand how amino acids translate into the coils, twists, and turns that make up a three-dimensional protein. This chemical shape determines how a protein will interact with its target molecule.

Thus far, like the authentic evolutionary process, most laboratory attempts to create evolution instantly have resulted in molecular disaster. Chemical yields have been greatly reduced and even a slight alteration to a protein can just as easily destroy its function as improve it.

But with computer technology continuously being improved, protein research in the future should unmask the mysteries we face today.

Computers Assist Scientists in Understanding the Structure of Proteins

The latest efforts by the Division of Computer Research and Technology (DCRT) to increase understanding of protein architecture involve computer visualization of proteins unfolding. Knowing how proteins fold is important because the solution to many molecular biological problems hinges on being able to build a model of a protein from its amino acid sequence.

In recent years, most of the work in molecular graphics has concentrated on modeling proteins by expanding on the results of X-ray crystallography. Although crystallography still is the only high-resolution source of three-dimensional information on protein structure, it is both expensive and time-consuming—taking a month or more to complete a single crystal structure.

Now, DCRT scientists are developing a new system that combines advanced computer equipment and mathematical software with biomedical expertise. A powerful piece of computer equipment called an array processor, which reduces the time needed to perform certain calculations, implemented with a molecular mechanics software program, has enabled the scientists to develop a graphic simplification of protein structure.

Two facts about protein folding are considered indisputable: a protein emerges from the ribosome unfolded as a polypeptide chain; and crystallography demonstrates that proteins are folded structures.

How does the polypeptide chain transform from the unfolded state to the folded state? Richard J. Feldmann and his coworkers at DCRT have developed computer images of the chains of atoms of the peptide backbones of proteins as revealed by their crystal structures. The distance and angles in the peptide backbone have been mathematically manipulated to create a smoothed chain that is easier to see in three dimensions.

By examining this smoothed crystal structure, the DCRT team asserts, it is possible to develop a logic that specifies protein folding paths. The logic is developed by working backwards from the folded state to the unfolded state. The essence of the idea is to determine whether a smoothed visualization of the protein's crystal structure offers any clues about the stages of protein folding.

Feldmann has used the analogy of rolling a ball of string. "Thinking about rolling up string into a ball," he explains, "we leap almost immediately to questions about how the stiffness of the string affects its manipulation." The computerized unfolding of the protein is simply a backwards view of the forward, folding (or rolling) process that occurs in nature.

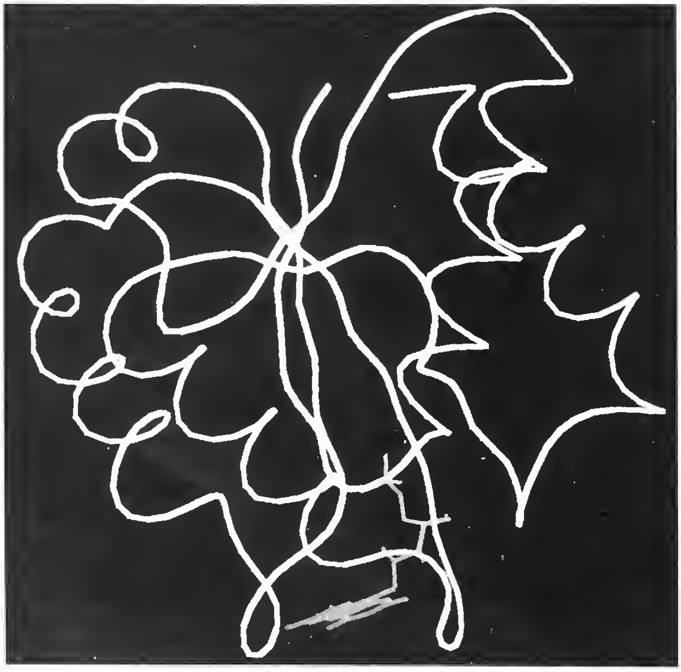
The analogy of the ball of string, Feldmann explained, "lies in the idea that portions of the protein as it folds must move about in three-dimensional space."

In the graphic simplification, the protein's peptide backbone is represented as a smooth, wire-like object. Other protein features are depicted in different colors and, thus, become clearly distinguishable as separate spatial entities.

This representation produces a curve in three-dimensional space for each protein, which connects the protein's features and forms its global structure, thereby enabling viewers to grasp the protein's structure almost independent of its size or complexity.

Until recently, discussions of protein folding have been conducted predominantly without graphic aids. So there is no appropriate vocabulary for discussing the newly visualized motion of chain-like objects in three dimensions. The development of such concepts, and the vocabulary to discuss them, is one goal of the DCRT work.

Realization of this goal is years away as is the scientists' hope of developing a way to create protein models by folding any protein sequence from first principles. Nonetheless, significant progress toward its fulfillment has been achieved this year. ■



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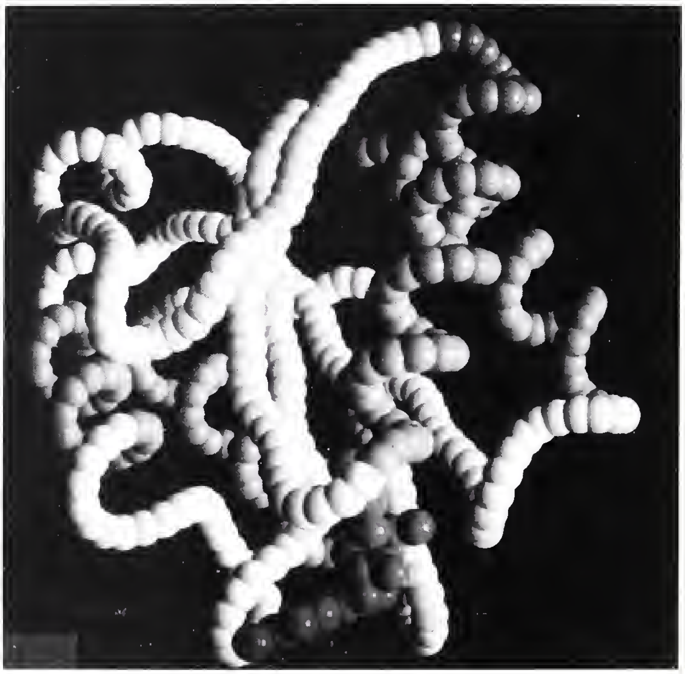

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Where crystal structures exist for members of a protein family, suitable computer graphic models can be constructed. However, with few exceptions, it is impossible to build a model when only the amino acid sequence is known, because it is not generally known how proteins fold.
DCRT scientists have developed a tool for understanding the folding of proteins; they have applied these techniques to all of the protein data sets in the Protein Data Bank from the Brookhaven National Laboratory. A set of three-dimensional slides of these has been prepared and distributed to scientists throughout the world so that they can begin to think about the folding of proteins in a more graphic way.
These two illustrations show the folded protein flavodoxin. The "wire" model is useful for studying the back of the protein; the model with filled-in spheres (color-coded) is useful for studying the characteristics of the surface.

Computer Techniques Make Possible the Measurement of Forces between Biological Molecules

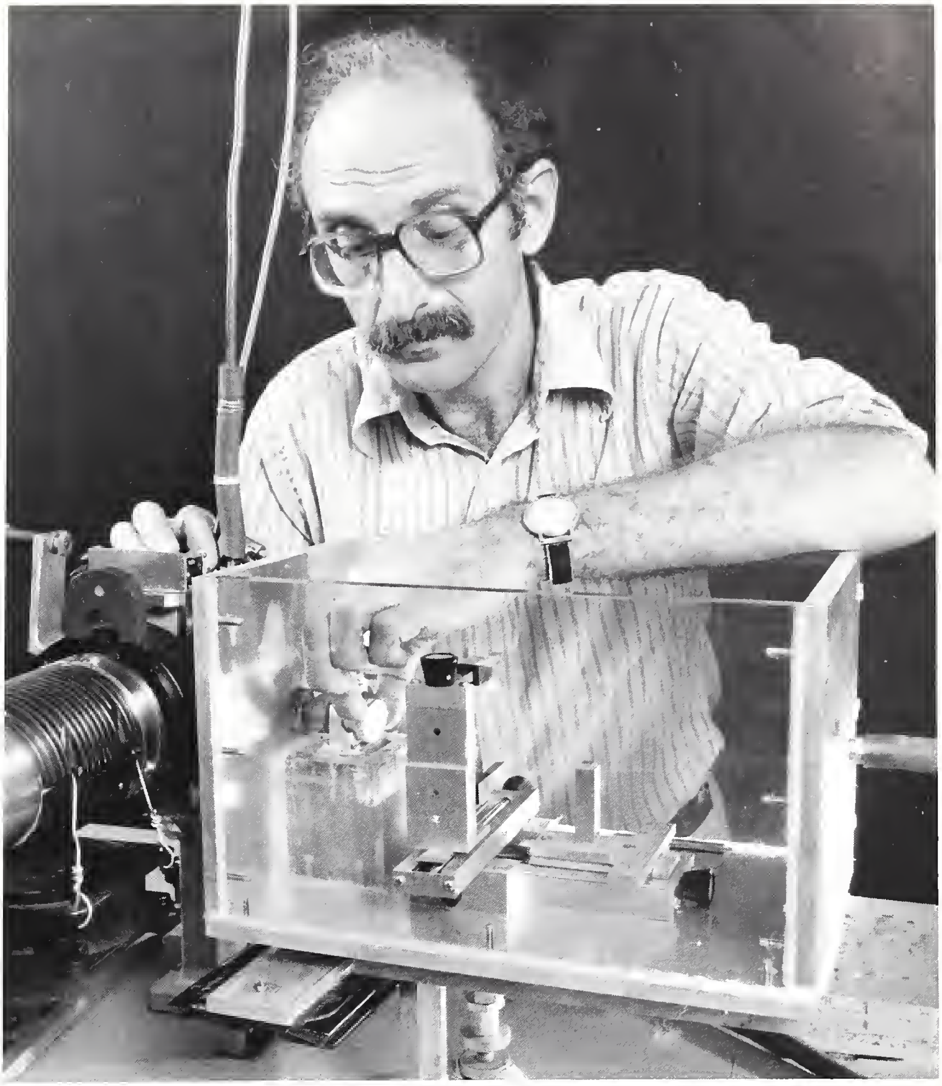
One of the great challenges in molecular biology today is to understand how the basic building blocks of life—proteins, nucleic acids, lipids, and carbohydrates—organize themselves into the cellular assemblies that are being defined through modern cell biology. To understand cell biology, scientists must understand the nature of physical forces that allow biological molecules to find each other and fit inside cells. The research needed for his work relies heavily on computer technology supported by the DCRT.

Until recent years, there has been surprisingly little direct information about molecular forces in aqueous media. The role of the water, in particular, surrounding two interacting molecules has been especially difficult to define. It has long been recognized that water has unusual solvent properties. These make force computation difficult and should make intermolecular forces themselves act in qualitatively different ways from those in most other media.

It now appears that one may think of water as being specifically patterned around the surface of soluble molecules, and the interaction of two molecules in water as a displacement of this patterned water as the two bodies approach. The action of this structured water between two molecules is called the "hydration force."

Present-day thinking in these terms began almost 10 years ago in a collaboration between Dr. Adrian Parsegian of the Physical Sciences Laboratory, DCRT, and the Laboratory of Chemical Biology at the former National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), and Dr. Peter Rand, Brock University, Canada.

These scientists developed an osmotic stress method for directly measuring the force required to push electrically neutral lipid membranes. They identified very strong replusive hydration forces between membranes even separated by 20 to 30 Angstroms, i.e., some 7 to 10 molecular diameters of water. This force easily dominated all other interactions, even electrostatic forces in the case of electrically charged interacting membranes. These scientists soon realized that hydration barriers in this range of separations were virtually ubiquitous among membranes and were an important factor in maintaining stable membrane structure. In fact, the loss of this repulsion in living systems, as when membranes are destined to fuse, is a closely regulated event involving deliberate changes in membrane structure, composition, and ionic environment.



V.A. Parsegian, Ph.D., places a DNA sample in the path of an X-ray beam, as part of his research in the direct measurement of physical forces between macromolecules. NIH PHOTO 2138

Recently, Dr. Donald Rau of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and Dr. Parsegian, with the assistance of Dr. B-K Lee of the DCRT, have succeeded in measuring the intermolecular forces between parallel DNA double helices. Again, the clear result is that the dominant forces between these molecules as they approach contact are forces of hydration, rather than the electrostatic forces that had been expected in this system.

It appears that the organization of the water directly in contact with the molecular surface can affect the structure of water many Angstroms away from the surface. Ion binding to the DNA surface, for example, changes the intermolecular force by modifying the organization of the water on the surface of DNA, due to the restructuring of water by these ions. Most recently, it has been found that specific ions so change the water at particular spots on the molecular surface that they allow the formation of "water bridges" between helices and the appearance of dominating hydration forces.

To achieve these results, the NIH scientists have used several different techniques, such as X-ray diffraction, computer graphics, and fairly sophisticated physical theory. For example, the Parsegian and Rand work was noted by the Yugoslav physicist, Dr. Stepan Marcelja (now at the Australian National University), who showed how water several layers away from the molecular surface can be influenced by the first layer of water in direct contact with the surface.

One theme of experiments in progress is to examine forces between molecules of known structure to be able to correlate measured forces with features of molecular architecture, as seen on the DCRT molecular computer graphics system.

Another theme is to look at the many biological processes that apparently involve changes in hydration of molecular surfaces caused by ion binding or controlled changes in surface shape or composition. In the biochemical sequence, accompanying the fusion process mentioned above and changing the membrane composition, for example, one finds that substances differing by a single metabolic step show qualitatively different affinities of water. Controlled biochemical changes in the membrane surface seem consequently to control membrane hydration and to modulate the hydration barriers that keep membranes stably separated.

Dr. Muriel Prouty, working with Dr. Alan Schechter at the NIDDK and with Dr. Parsegian, has examined the aggregation of abnormal sickle cell hemoglobin viewed as a process of molecular dehydration.

Dr. Joshua Zimmerberg of the DCRT and Dr. Parsegian are measuring changes in the aqueous volume within transmembrane ionic channels that control the flow of materials in and out of cells. These measurements are intended to provide a means to unify structural and ionic transport approaches to understanding channel activity. These scientists are particularly interested in defining the role of hydration within channels in controlling the selectivity of the material that is transported through a particular channel.

There are several reasons why computer technology makes this work possible. Models of the molecules under study are drawn by computer. Computer analysis is necessary to understand the physical basis of the forces in question. Complex mathematical calculations yield information about the nature of the forces. And the measurement of forces provides information for the computation and modeling of molecules, and ultimately, of molecular assembly. ■

Electron Microscope Imaging System Uses Computers to Perform Chemical Analysis

Joyce F. McCarthy

Few laboratories in the world can do the microanalysis performed by the electron microscope imaging system at NIH. A joint effort by NIH physicists, engineers, and computer scientists has created a unique system with a spectrum of capabilities flexible enough to deal with a broad range of experiments.

Online since 1982, it is the result of 4 years of intensive work by a project team formed from the Division of Computer Research and Technology (DCRT) and the Division of Research Services (DRS). Physicists, engineers, and computer scientists from DRS' Biomedical Engineering and Instrumentation Branch and

Dr. Richard Leapman uses the electron microscope imaging system to analyze biological samples. Here, he prepares to analyze a pancreatic cell. NIH PHOTO 2139

DCRT's Computer Systems Laboratory collaborated to develop this complex, sophisticated technology.

The system includes an analytical electron microscope, electron beam X-ray microanalyzer and several computers. It correlates a specimen's microstructure with its microchemistry on a scale down to a hundred atom diameters and is the only system of its kind in the United States. Only a few laboratories in the world can perform the specific type of chemical microanalysis done here; moreover, the spectrum of capabilities of the new NIH system is unique.

Incorporating electron beam instruments with X-ray and electron energy-loss detectors, the new analytical system chemically analyzes a specimen. Digital computers collect and process chemical structural data and produce an image on a color display. Colors in the image represent the distribution of different elements in the specimen.

The specimen is introduced into a high vacuum column of the electron microscope and secured with an air lock device similar to that used in a space capsule. The electron beam is scanned under computer control over a region of the specimen being studied, while selected signals (spectra) acquired from many thousands of points in the specimen are stored directly in the computer rather than on a photographic media as in a conventional electron microscope.

These stored signals are then processed to produce images on a color display to permit correlation of elemental distribution and morphology. Under computer control, a number of signals can be recorded simultaneously to obtain images of the distributions of all elements in the periodic table except hydrogen and helium.

The digital computer is crucial to the analytical imaging system. Its speed and storage capacity make possible the high speed acquisition and the complex mathematical manipulation of the huge quantity of chemical elemental data generated as the electron beam is electronically scanned over the specimen.

Major effort was put into designing software that is both easy to use and flexible enough to deal with a broad range of experiments.

The analytical imaging system can be applied to a variety of research problems. For example, NIH scientists have used the system to investigate such problems as: trace elements in neurological diseases, such as Parkinsonism-dementia, amyotrophic lateral sclerosis (ALS)and Alzheimer's disease; the role of ionic concentrations in cystic fibrosis; the role of calcium in neuronal synaptic transmission; elemental identification of respirable particles, such as coal dust and asbestos found in lung tissues; and the formation of hard enamel in teeth.

Computer system hardware and software modifications to the electron microscopes and methodologies for actual specimen analysis all were developed by members of the DCRT/DRS team. ■

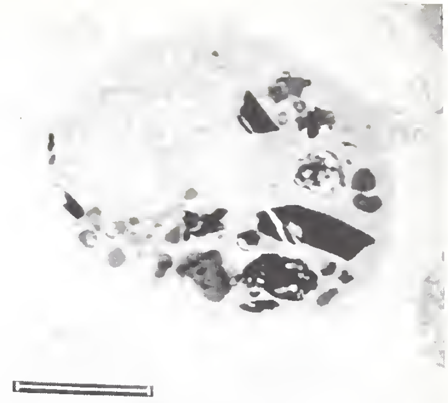
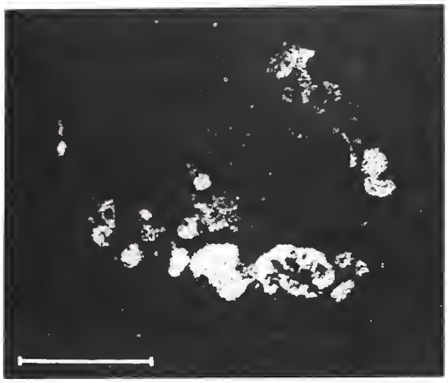
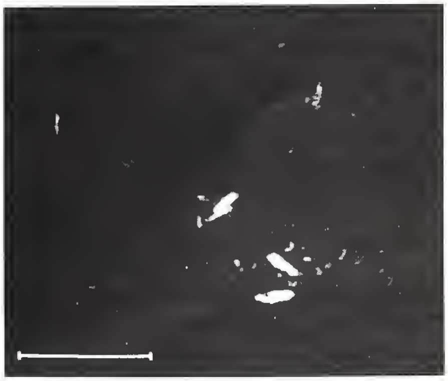


Image of pathological human lung macrophage obtained through scanning transmission electron microscopy, one of the capabilities of the new imaging system. NIH PHOTO 2141



X-ray map showing deposits of iron in the macrophage. NIH PHOTO 2142

The collaborative group who developed the electron microscope imaging system includes, standing (l to r): Dr. Richard Leapman, Dr. Henry Eden, Carter Gibson, James Del Priore; seated (l to r): Keith Gorlen, Dr. James Ellis, Charles Fiori and Carol Swyt. NIH PHOTO 2140



X-ray map showing silicon inclusions. NIH PHOTO 2143

Image Processing Yields Valuable Biomedical Information

By using a multidisciplinary approach to molecular biology, an innovative, state-of-the-art image processing facility has been created that exposes new horizons in the biomedical world.

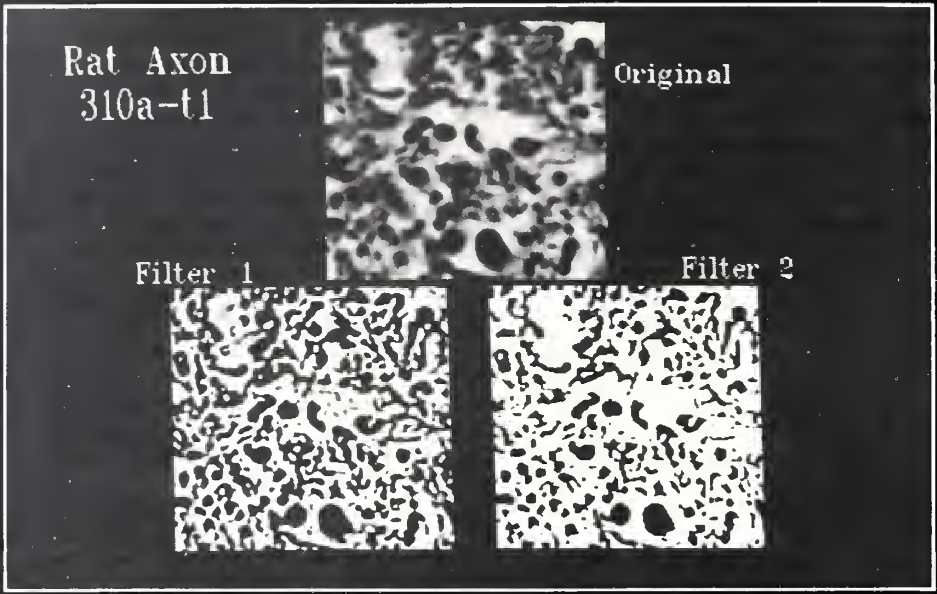
The Image Processing Facility at the National Institutes of Health (NIH) aids researchers in extracting from biological and biomedical images information that could not be obtained without sophisticated computer hardware and software techniques. Image processing uses computers to quantitate or compare images, allowing researchers to better understand pictorial data.

DCRT researchers collaborate on numerous projects that use advanced computer methodology to analyze important macromolecular structures including viruses, components of connective tissue and muscle, and protein sequence data. Viruses, which are not visible under a light microscope, are perfect candidates for image processing.

These structural studies are primarily basic research in orientation and results, but lay the groundwork for further analyses and experimentation of a possible applied or clinical nature. In addition, algorithms—a type of calculation process needed for this work—have been developed by the DCRT and are published in major scientific journals and widely distributed to the scientific community at large.

Other researchers at NIH collect data from magnetic resonance scans or computed tomography, apply algorithms, and create three-dimensional images, allowing them to better visualize and interpret their data.

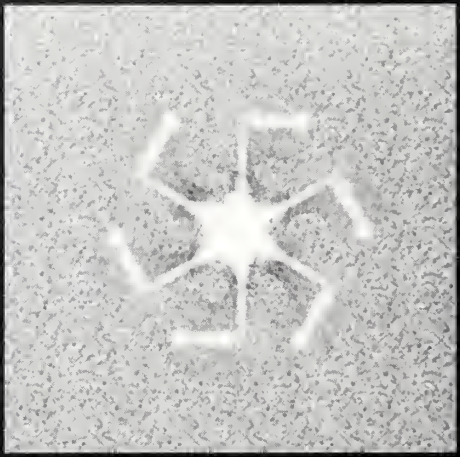
More than 100 NIH investigators use image processing technology in clinical studies, graphics, laboratory imaging, microscopy, and three-dimensional imaging to assist them in obtaining valuable biomedical information. The following examples illustrate the range of information available from image processing.



This electron micrograph is used to help study spinal cord injury in children. The image processing technique involves quantifying the micrographs by counting the axons in a rat model pre- and post-trauma. The computer processes the original image in such a way that only the axons remain in the image. The system then counts them and computes the percent of the total that is composed of axons.

For the first illustration, a filter is used to sharpen the initial image. In the second illustration, another filter cleans up the micrograph to facilitate quantitation. NIH PHOTO 2144

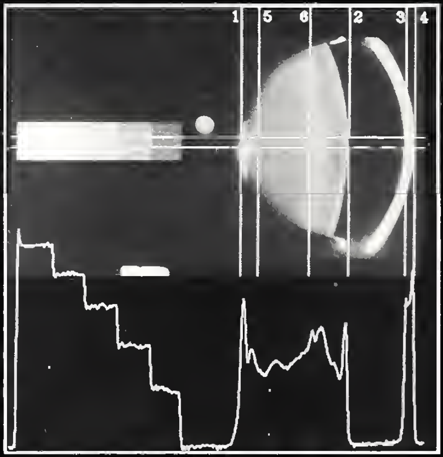
Images provided by M.A. Douglas, Division of Computer Research and Technology (DCRT), a collaborative study with Dr. Dennis Johnson, Children's Hospital, Washington, D.C.



An electron micrograph of a "tail" of bacteriophage T7 imaged at high resolution. This picture was computer-processed using correlation averaging methods, where multiple images are put together mathematically with computers to create a composite photo. This technique reduces the extraneous components in the photo, producing better resolution of the virus.

The six protruding fibrous proteins are responsible for recognizing specific sites on the surface of susceptible cells, thereby initiating the infection process. NIH PHOTO 2145

Image provided by B.L. Trus, Ph.D., Division of Computer Research and Technology (DCRT) in collaboration with A.C. Steven, Ph.D., National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS), M. Unser, Ph.D., Division of Research Services (DRS), J. Maizel, Ph.D., National Cancer Institute (NCI), and F.W. Studier, Ph.D., Brookhaven National Laboratory.



A special microscope with a slit-beam is used to study the lens of the eye in cataract patients. It allows scientists to obtain a cross-sectional image of the eye, not possible with other methods of photography. A computer is used to quantitate the differences in the images between a normal eye and one with a cataract. Note the posterior subcapsular cataract (near line 1) at the rear (left) of the lens of the eye. The plot is a one-dimensional representation of the optical densities in the center of the eye, which provides more precise information on the progression of the cataract over time. NIH PHOTO 2146

Image provided by B.L. Trus, Ph.D., Division of Computer Research and Technology (DCRT) in collaboration with M.B. Datiles, M.D., and P.A. Edwards, M.D., National Eye Institute (NEI), and Sylvan B. Green, M.D., NCI, formerly NEI.

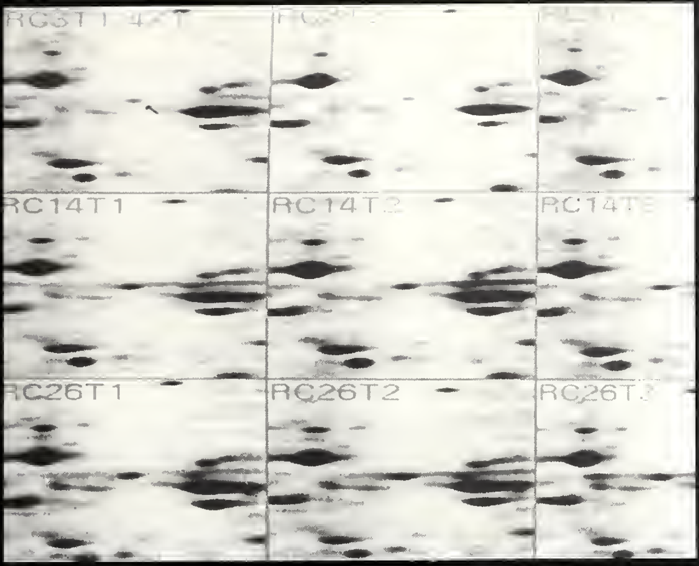


Figure I NIH PHOTO 2147

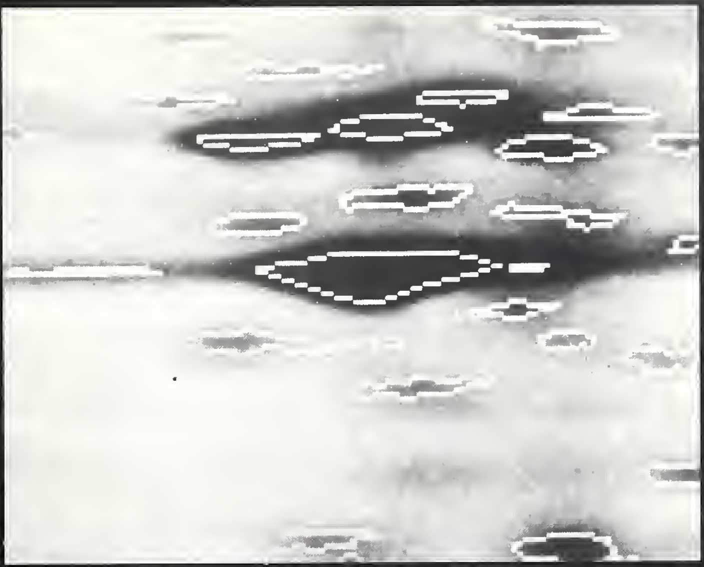


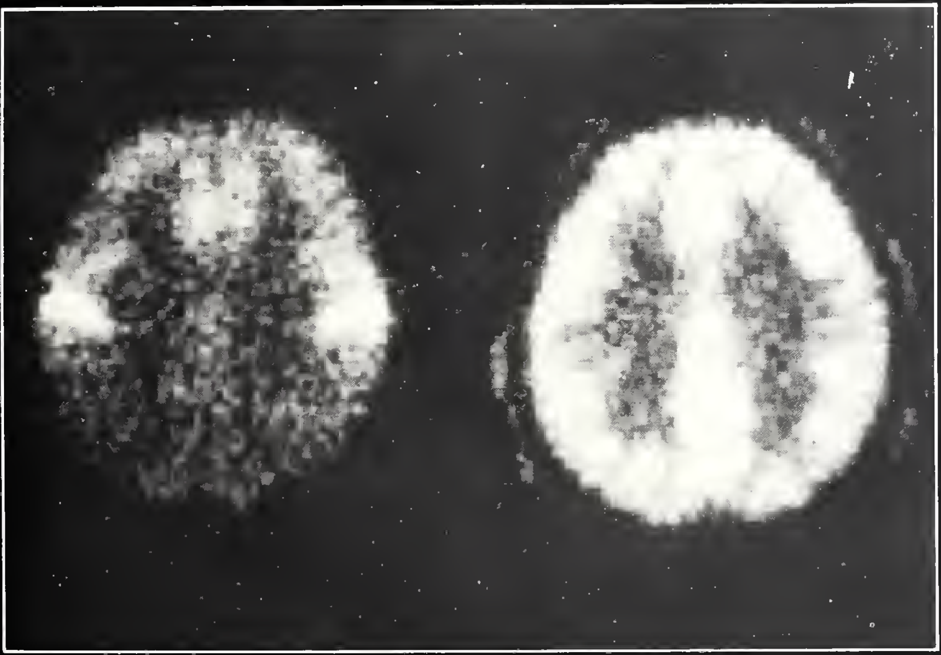
Figure II NIH PHOTO 2148

The ELSIE III gel analysis system is being used to identify polypeptides associated with the neoplastic process. Two-dimensional gel electrophoresis (a technique to separate materials using an electric field) allows for the simultaneous analysis of thousands of proteins on a single squared gel. Radioactively labelled amino acids are incorporated into cellular proteins and separated on the gel. A radiographic image is produced and then scanned with a computerized device to detect the radioactive spots on the gel and their intensity, thus the presence of protein and its amount in each spot. The computerized system automatically matches the patterns of spots which represent protein synthesis. Thousands of proteins can be followed this way to examine any abnormalities in protein synthesis, which may indicate an association with the cancer process.

Figure I displays some of the protein spots found by the system. (The spots are outlined in white.)

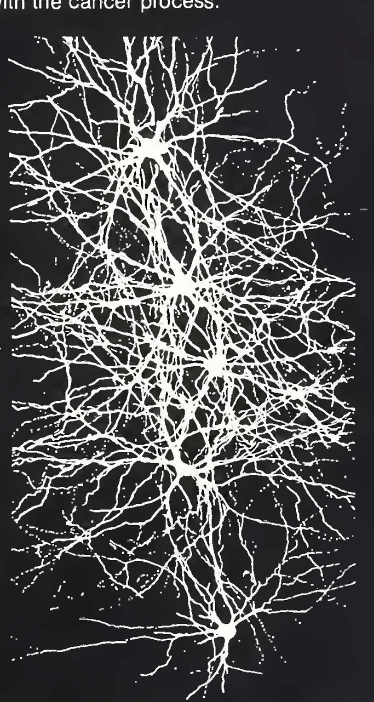
Figure II shows a mosaic of the region surrounding the same spot in nine different gels. This allows the same spot to be followed through a series of gels.

Images by Mark J. Miller, Ph.D., National Cancer Institute (NCI).



Comparison of advanced Alzheimer's Disease (L) and age-matched control (R) using Positron Emission Tomography (PET). PET provides information not only about the structure but also the function of the brain. The technique involves injection of a radiolabelled chemical—a positron emitter—into the bloodstream. Using positron emitters, hundreds of chemicals of biologic importance can be labelled. The PET scanner consists of a series of detectors positioned around the patient's head to collect the radiation given off by these isotopes with short half-lives. A computer provides information on the concentration and amount of the chemicals and translates the radioactive density into a map of the distribution for a particular biological molecule, in this case glucose, into an estimate of its metabolism by the body. In addition, statistical differences between the images are compared to see if they are significant and predictive of disease patterns. In this photo, the advanced Alzheimer's brain shows decreased regions of glucose metabolism compared with the control brain. Using this technique, scientists hope one day to be able to diagnose defects in the brain before they are translated into behavioral abnormalities. NIH PHOTO 2149

Image by Howard Burrows, Ph.D., National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

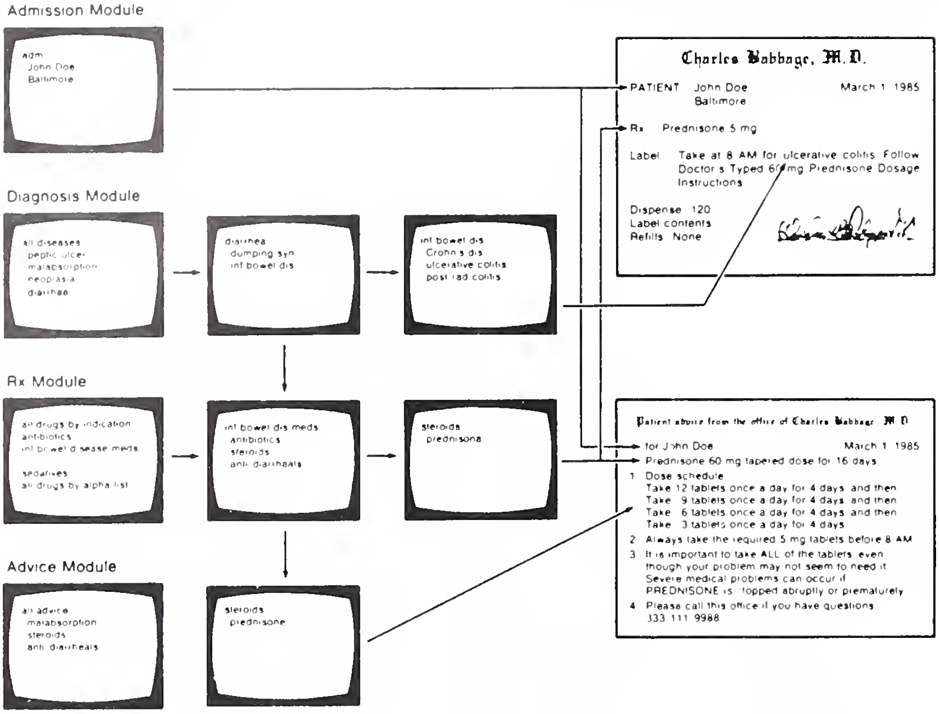


Photomicrographic montage of the cell bodies and proximal dendritic trees of five spinal motoneurons for spinal cord studies. Images of five serial sections are taken with a light microscope, then computer-processed to reconstruct in three dimensions. An entire cell can be reconstructed from 40 such sections. The computer assimilates information relevant to the length and diameter of the dendritic branches and uses it to determine how the dendrites are involved in integrating synaptic information. These studies are useful in investigating how the shape and size of various parts of the motoneurons are related to the muscle fibers they control. NIH PHOTO 2150

Image provided by Robert E. Burke, M.D., National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

Computers Handle Complexities of Prescription Writing More Efficiently

Angela Martin



Charles Babbage, M.D.

PATIENT John Doe March 1 1985
Baltimore

Rx Prednisone 5 mg

Label Take at 8 AM for ulcerative colitis Follow Doctor s Typed 60 mg Prednisone Dosage Instructions

Dispense 120
Label contents
Refills None

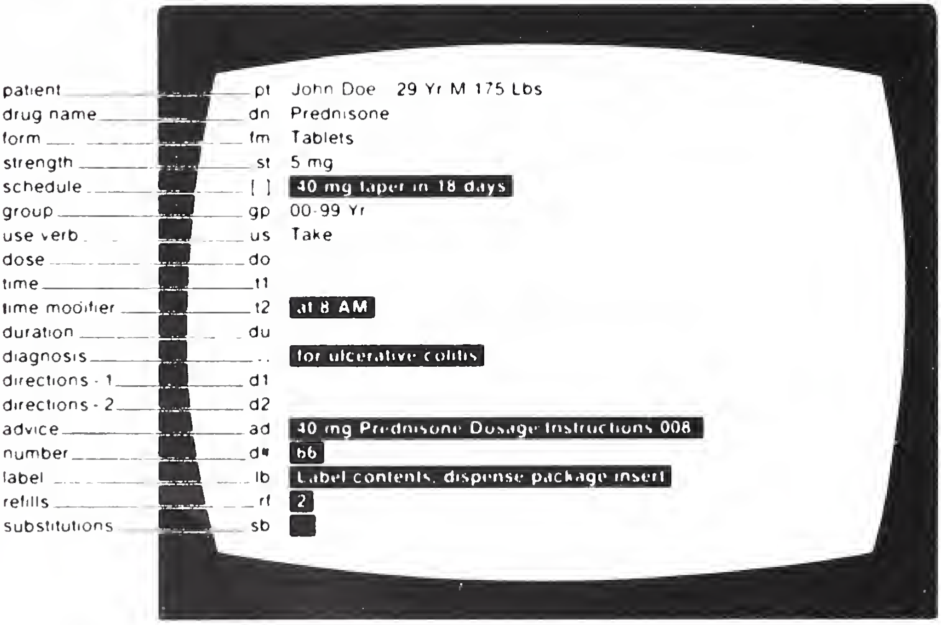
Patient advice from the office of Charles Babbage M D

for John Doe March 1 1985
Prednisone 60 mg tapered dose for 16 days

1 Dose schedule
Take 12 tablets once a day for 4 days and then
Take 9 tablets once a day for 4 days and then
Take 6 tablets once a day for 4 days and then
Take 3 tablets once a day for 4 days
2 Always take the required 5 mg tablets before 8 AM
3 It is important to take ALL of the tablets even though your problem may not seem to need it Severe medical problems can occur if PREDNISONE is stopped abruptly or prematurely
4 Please call this office if you have questions 333 111 9988

To create a prescription, the patient's relevant information is typed in followed by selection of the diagnosis, selection of relevant drugs for therapy, and patient's instructions, if needed

NIH PHOTO 2151



patient	pt	John Doe 29 Yr M 175 Lbs
drug name	dn	Prednisone
form	fm	Tablets
strength	st	5 mg
schedule	[ ]	40 mg taper in 18 days
group	gp	00-99 Yr
use verb	us	Take
dose	do	
time	t1	
time modifier	t2	at 8 AM
duration	du	
diagnosis	..	for ulcerative colitis
directions - 1	d1	
directions - 2	d2	
advice	ad	40 mg Prednisone Dosage Instructions 008
number	d#	66
label	lb	Label contents, dispense package insert
refills	rf	2
substitutions	sb	

The program uses a standard prescription template with abbreviations of prescription variables on the left and text phrases on the right NIH PHOTO 2152

In few areas of clinical medicine is there such an intense concentration of fact and numerical data as exist in a drug formulary. Because the computer is unsurpassed for data storage and manipulation, it is an ideal tool for expediently managing the complexities of prescription writing. Until recently, however, a simple and acceptable means of generating prescriptions by computer has proven an elusive goal. Now, new technology and the widespread use of personal microcomputers has turned this dream into reality.

A computerized system for writing and recording drug prescriptions and patient instructions has been developed by DCRT's Computer Systems Laboratory and used successfully in a Bethesda, Maryland dermatologist's office for the past two years. Simplicity and ease-of-use are important characteristics of the prescription-writing system, which allows detailed prescriptions to be generated on computer terminals placed unobtrusively in the doctor's consultation and treatment rooms.

The computer equipment used with this program includes a microcomputer (a complete, tiny computer system whose main processing blocks are made of semiconductor integrated circuits) and three high-speed video terminals with keyboards located in the treatment rooms. A letter-quality printer produces prescriptions on standard-sized prescription blanks that are supplied in perforated, fan-folded strips of 5,000.

A major feature of this program is the personal drug formulary that the physician extracts from drug compendia. The individual drugs and drug groups are indexed by conventional therapeutic groups and cross-indexed by disease groups, allowing the doctor to select from small lists of medications that have been preselected for specific diagnosis.

Individual drugs in the formulary are stored in an alphabetic text file and can be updated using a standard text editing program. Each drug product record is organized in a tree-structured format with up to five subordinate levels: drug formulation, therapeutic indications, dosage criteria, available strengths, and package sizes.

For example, a drug may have one or more drug formulations for different routes of administration. Each formulation may have one or more therapeutic indications for different disease states and may have one or more drug strengths or concentrations for its principal ingredient. Each drug strength may have one or more standard package sizes or specified dispensing amounts. Prescribing comments may be inserted at any level to be viewed by the prescriber or printed for the patient.

Creating a Prescription

To create a prescription, an office assistant types the patient's name, address, date of birth, sex, and weight into the computer using the full alphabetic keyboard. The doctor then begins the program by video screen selection of the diagnosis, which need not be definite, only presumptive. Scanning a list of tree-structured diagnoses, the doctor makes the specific diagnosis selection. Uncommon or complex diagnoses that are not stored in the computer can be typed on the full keyboard or handwritten later in space reserved for this information on the prescription form.

After selecting the diagnosis, three options are available: preselected lists of anatomic treatment sites, relevant drugs for therapy, or pertinent sets of patient instructions. Neither the diagnosis nor an anatomic site must be selected to generate computerized prescriptions, but including this information on a prescription label increases its specificity and reduces the chance for improper use. However, the information may be deleted or a built-in symptomatic phrase such as "for itching" or "for pain" may be substituted.

The program uses a standard prescription composition template that contains abbreviations of prescription variables on the left and text phrases on the right. Common options—such as generic drug name, optional commercial brand, drug form, strength, dose, frequency of administration, and duration of use—are automatically filled in to simplify handling of routine prescriptions. Thus, when a specific drug is selected, the display shows a choice for each of the prescribing options and automatically alters the dependent variables, such as strength and package size, for the selected option.

Two calculations that are unique to oral medications are included in the computer program—the dispensing amount and the usual dosage range. When a dose, frequency, and duration of therapy are given, the computer calculates the required amount of oral drug to be dispensed. The computer displays a usual dosage range that serves as a prescribing guide and also checks each prescribed single, daily, and cumulative dose against any stored limits based on the age or weight of the patient.

Drug-related instructions may also be printed when a drug is prescribed. This feature is useful in cases when the prescription label is too small to accommodate all needed directions or the patient is not likely to understand or remember dose and time relationships. For example, sometimes the drug treatments are complex, especially when several agents are used together. The prescription format contains a line, "Follow doctor's typed instructions." The linked instructions will automatically be printed with the prescription unless the advice line is deleted. Over 50 sets of medication-related instructions are provided.

Instructions about specific diseases may also be dispensed. Explanations of some disease processes are not readily understood or remembered by the patient. Therefore, approximately 100 sets of diagnosis-related material have been prepared to provide patients with adequate printed information on such factors as causation, communicability, and expected outcome. Diagnosis-related instructions may be printed without any reference to a prescription.

When all prescriptions and sets of instructions have been ordered, the computer is then given the command to "print." The doctor must sign each prescription form in the printed batch. Following the printing, the computer abstracts pertinent data to produce a therapy summary, which is printed for insertion in the patient's record.

System Accepted by Patients and Health Professionals

Patients appreciate readable prescriptions and lucid printed instructions. Few patients comment on the video terminal in the treatment room, most accepting it as a routine tool. Since the keyboard operation is nearly silent, the video terminal, if properly placed away from the patient's direct view, is not seen as a mechanical intruder.

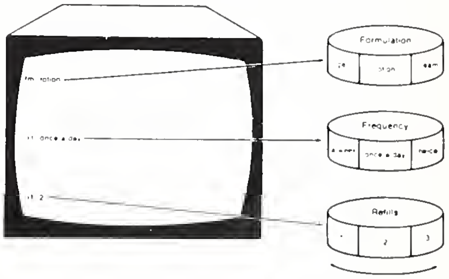
Pharmacists like the program because prescriptions are concise, complete, and legible, thus reducing the need for telephone calls to clarify questions regarding refills, substitutions, or prescription uncertainties. Cryptic Latin abbreviations are replaced by intelligible English phrases for even greater clarity.

Doctors find the automated prescription process saves time, as most computer prescriptions are prepared in about 20 seconds. Although some routine prescriptions can be handwritten faster, the overall prescribing process is quicker and more efficient with the computer, because the machine also abstracts the prescription for the office record and conveys therapeutic details to patients. The need to refer to drug compedia is reduced because the program itself contains most needed information on drug administration and dispensing. Almost all prescriptions can be machine-produced; only occasional complicated dosage schedules must be typed or handwritten to tailor the drug dose to a patient's needs.

Nurses, office assistants, and medical students can learn the system quickly, and with proper guidance, they can generate routine prescriptions or patient information supplements. Regardless of who generates the prescription text, the doctor maintains ultimate responsibility, because no prescription can become a legal document without an authorized signature.

The computerized prescription-writing system even seems to improve doctor-patient communications. The availability of printouts containing explicit treatment instructions enables the doctor to highlight important aspects without explaining every detail. Thus, the doctor writes and lectures less but listens and counsels more; and the number of telephone calls from patients seeking more information is reduced. Better therapeutic results are also achieved because of improved patient compliance.

Experience shows that computerized prescription writing offers many advantages. As more and more doctors invest in office-based microcomputer systems, it may well become the way of the future. ■



Specific drug information, such as different formulations as well as frequency of administration and refills, are included in the computerized system. NIH PHOTO 2153

Computer Networking at NIH: An Advance Whose Time Has Come

Dickey Wilson

At NIH, computer networking is providing a strong foundation for scientific and academic activities. From the scientists' perspective, networking will speed and simplify administrative tasks, improve patient care, expand communications not only on the NIH campus but throughout the world, broaden and enhance collaborative efforts, and encourage exchange of ideas and information.

An Overview of Networking

Networking—the linking of computer equipment and computer users to one another—is the latest advance in data processing to find general application among unsophisticated computer users.

Networking enables people to send information—messages (or "mail"), research papers, data—electronically to other computer users. Networks provide a simple way for users to gain access and use a variety of computers and computer equipment with a single connection to a cable. Finally, networks allow computer-to-computer data transmission.

Description and History of Networks

Simply speaking, a network is a combination traffic and transportation system that moves signals from one point to another. It controls the speed, direction, and frequency of signals. For decades, our lives have been enhanced by telephone, radio, television, and telegraph networks.

While the first network connectors were wires, today the primary signal transmission media are coaxial cable, microwave, satellite link, and most recently, fiber optic cable.

As communications technology has evolved, the use of networks to move computer-generated data has increased. Originally, the computer industry was a user of network technology; now it is a key contributor. For example, the first satellites were simple reflectors that bounced signals back to earth; now, communications satellites include complex computers that perform some of the traffic control functions.

Advances in computer technology have made this possible, particularly the ten-fold increase in computer processing speed in the early 1980s. An indicator of the rapid advances in satellite technology is the fact that, in 1965, an INTELSAT satellite could handle 500 voice circuits; by 1980, this capacity had increased to more than 10,000 circuits per satellite.

Benefits of Networking

Networking provides many benefits. One benefit is speed; without networks, getting research papers or laboratory data from one distant point to another involves copying a document or computer tape and mailing it, a process that can take 24 hours by courier, a week by domestic mail, and a month or more by overseas mail. In contrast, networks can move data within minutes or hours.

A second benefit is dependability; if an envelope or package is lost or misrouted, the material may never reach its destination. With a network, if information gets lost it can be retransmitted immediately.

A third benefit is cost effectiveness. With networks, resources can be pooled so that several people can share equipment. For example, instead of spending $3000 to acquire a dot-matrix printer for each of 10 personal computers (PC's), an organization can network the PC's and buy a faster, more sophisticated laser printer for $2500. In this example, users have access to much better equipment at a lower total cost. Disk drives, plotters, and other equipment can also be shared.

Finally, for researchers who use computers for data analysis, probably the most important benefit of networks is that large volumes of computer data can be sent quickly, dependably, and easily. This enables two or more researchers to share and analyze data simultaneously.

Types of Networks

Large-scale commercial networks, such as TYMNET and TELENET, use telephone, microwave, and satellite technology to move information. For a fee, these networks can provide national and international telecommunication. Users gain access to these networks through

After assessing overall campus networking requirements and reviewing the available technology, DCRT engineers designed a pilot Local Area Network linking IBM PC's in two adjacent buildings. Timothy Kuhfuss (l) and Ronald Fico (r) review the network plans. NIH PHOTO 2154 the telephone system. Although high-speed transmission is possible on these networks, most users find the least expensive, lower-speed options adequate.

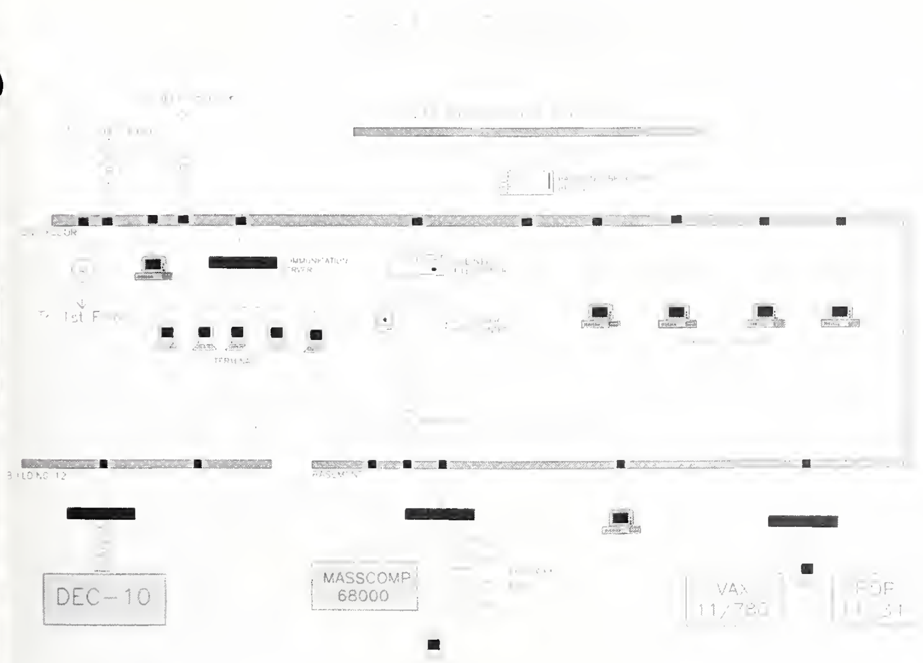
Local Area Networks (LANs) are intra-organization, privately owned networks, with a limited geographic scope. LANs usually use cable—which can transmit data at very high speeds—to link PC's and other equipment. Even though fiber optic cables are the highest-speed medium, they are generally difficult and expensive to install. Therefore, most LANs use coaxial cable or telephone lines as the data transmission medium.

Depending on its design, LAN transmission technology is classified as baseband or broadband. Baseband technology allows only one signal to travel along the cable at any given time; broadband allows transmission of many signals simultaneously.

Network Components and Their Functions

A typical computer network that links two people sitting at PC's has several basic components. In a network using telephone connections, these include the information sender (the person sending information), the input device (PC and its keyboard), the transmitter (modem), the channel that carries the transmission (telephone line or other transmission medium), the receiver (modem), the output device (PC and its screen or printer), and the information receiver (the person receiving information). (In a network that links two computers, the sender and receiver are computers, not people.)

One additional network component is the computer programs or software. To function, a network needs software to oversee all of the other components and provide overall control. Computer equipment manufacturers (IBM, DEC, etc.) sell standard, general-purpose network software. ARPANET was designed specifically to connect research computers.



This pilot Local Area Network interconnects computer terminals, systems, and modems throughout DCRT. Networks like this could one day be interconnected to others at NIH in a campus-wide network. NIH PHOTO 2155

Before signals are transmitted through a network, they must be manipulated so that they conform to a standard. For example, before a computer's digital signals are sent through the telephone system they must be converted to analog signals. This signal translation requires a modem (modulator/demodulator), which alters the amplitude, frequency, phase, and pulse of digital signals, then sends the signals; at the receiving end of the network, another modem restores the original (digital) characteristics of the signals.

Office Automation and Bulletin Boards

Many organizations use networks for office automation functions, including electronic mail and meeting scheduling.

As realized in electronic mail, a benefit of networks in comparison with telephone conversations is that computer networks can store messages until the receiver is ready to review them. This can eliminate "telephone tag" and allow users to send, receive, and respond to messages or questions as quickly as possible.

Some office automation systems help users schedule meetings. The system stores a calendar for all users. To set up a meeting, a user checks the calendars of all proposed participants to find a convenient date and time, blocks out that time slot on everyone's calendar, and uses electronic mail to send everyone a notification of the meeting.

Another common use of networks is electronic bulletin boards. As with three-by-five cards hung on a wall, messages on the electronic bulletin board can be read by all users. Bulletin boards are often set up by groups of people with a common professional or personal interest. One might focus on solutions to complex scientific problems. Another might be oriented toward exchange of ideas; people are invited to participate by contributing opinions or information.

The best-known use of bulletin boards, however, is exchange of public domain PC software. Users transmit programs they have developed, making them available to others. Programs range from spreadsheets to simple inventory or billing software. A telephone and modem give PC users access to most bulletin boards.

Networking at NIH

Over the last two decades, DCRT has developed a variety of computer networks for NIH scientists. The earliest of these were the so-called "star" networks, in which computer users or smaller out laying computers communicated to and through a larger central computer. For example, in the early 1970s several dozen scientists in a single NIH building had their major analytical instruments all connected to a central, medium-sized minicomputer by a network of small microcomputers.

On a more massive scale, thousands of NIH scientists were able to use or exchange experimental data and leave mail messages for each other. These scientists could do this because they used the NIH Computer Center over standard "dial-up" telephone lines from their laboratories and offices. NIH scientists in Arizona or North Carolina could use this facility as easily as those in separate buildings on the NIH campus in Bethesda.

The NIH Computer Center then networked to other computer centers of the Food and Drug Administration (FDA) and more recently became part of an international network called Bitnet. (see later in story)

DCRT is now in the third year of a long-range networking plan for NIH. Although NIH staff currently use several different LANs and telephone-based networks, there is no overall interconnection between the users of the LANs. On- and off-campus users can dial up and connect with NIH's IBM mainframe. Several departments have installed minicomputer and PC LANs, some of which connect components in two or more buildings.

A campus-wide network would encourage the sharing and dissemination of information by interconnecting scientific and engineering computers, workstations (terminals and PC's), and LANs.

After assessing overall campus networking requirements, and reviewing the available technology, DCRT engineers designed a pilot LAN linking IBM PC's in two adjacent buildings. Staff identified many appropriate applications of medical data and image transmission, including transmission of electron microscopy and magnetic resonance imaging (MRI) data.

At present, DCRT engineers are helping individual departments install LANs so that they can communicate internally. Eventually, these individual LANs could be interconnected in a campus-wide network.

DCRT's Pilot LAN

In 1985, DCRT chose 3COM Corporation's Ethernet software and PC boards for its pilot LAN. In this network, several PC's are designated servers (a server is a special computer that allows users to share the equipment attached to it, such as disk space, printers, and plotters).

Currently, the pilot LAN connects almost 100 microcomputers and 5 minicomputers in 3 NIH buildings. PC users on the LAN use electronic mail and share data generated from a wide variety of software packages.

A calendar system for scheduling meetings was recently added. The LAN has five printers available for shared use, including high-speed, letter-quality laser printers.

Network users have been testing 3COM's net network software (III Plus) and a network version of Ashton-Tate's dBASE III Plus, and network administrators expect to install both in the next few months. III Plus will allow similar 3COM Ethernet networks to communicate with each other over telephone lines.

DOware—A New Tool for Personal Computer Networks

Doware is a user-friendly computer system designed to aid the novice, as well as the experienced IBM Personal Computer user in communicating with a 3COM Ethernet network.

Developed by DCRT's James Del Priore, DOware is an enhancement to the popular Ethernet, a commercial system for networking personal computers.

DOware is unique in its simplicity of use. All commands have a common and consistent syntax. They all start with the word "DO" followed by the desired function: typical functions such as DO PRINT, DO MAIL, DO HELP, and the convenient DO 411 (for user information) and DO 911 (for emergency help).

Because of the built-in help features, users can become proficient in DOware with no training. A new user can simply type in DO TOUR to get a guided tour around the network.

"DO" commands support all existing EtherSeries and III Plus functions including many new features added by the DOware system.

Special software known as DOware was created by James Del Priore (r) to provide easy access to DCRT's Local Area Network for users such as DCRT librarian, Ellen Chu (l). NIH PHOTO 2156

BITNET—An International Scientific Network

Imagine that you have just finished preparing a speech describing research you have been doing over the last five years, and you have just learned that a colleague in Switzerland has some additional information that could add a new and important perspective to your work. Your speech is two days from now, and you would like your Swiss counterpart to review your findings. How do you get a copy of your paper and your data—both stored on personal computers—overseas quickly? If you send them by international courier, what happens if they are lost or misrouted?

Or imagine that you have done a study of the effects of diet on life expectancy, and collected data on more than 500 patients nationally. A colleague, who works across the country, has conducted a similar study and suggests you pool your data and collaborate on a paper. Your extensive data are stored on your institution's mainframe computer. How do you and your colleague share your data and collaborate on the statistical analysis?

Perhaps you are about to perform emergency brain surgery on a patient, but you want another specialist across the country to review the CT scans. How can you get the CT images to the specialist quickly enough?

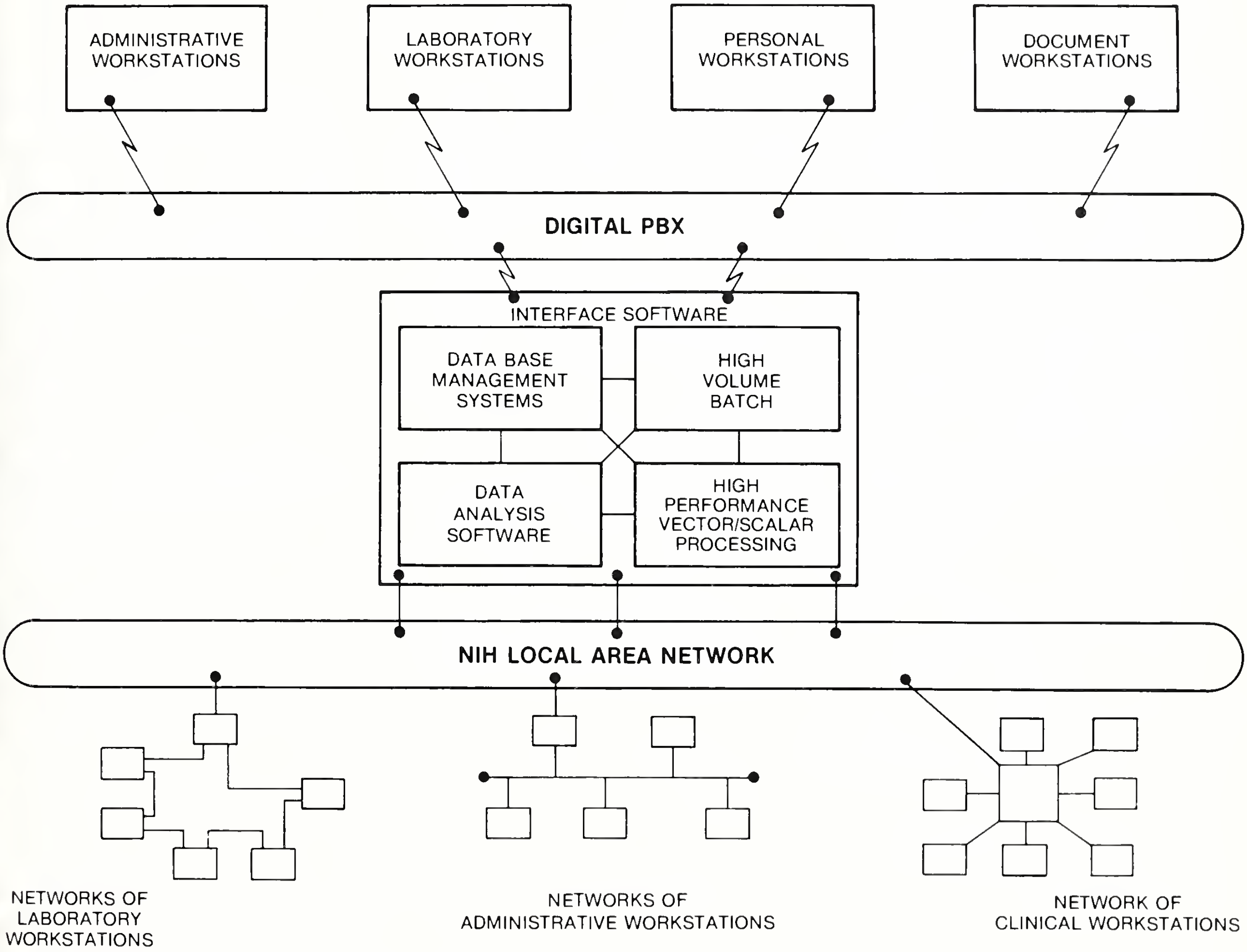
BITNET may be the vehicle you need. In July 1986, NIH joined the BITNET international network. BITNET allows scientists and educators to exchange messages, mail, and files (or documents).

BITNET was established specifically to enhance worldwide communication and collaboration in the research and academic communities. Connecting more than 1200 computer centers in research organizations, and in universities and other educational institutions, BITNET gives users access to the EARN (European BITNET) and NETWORTH (Canadian BITNET) international networks.

There are no registration fees for using BITNET. Each user has the responsibility to store and forward information.

NIH scientists have already taken advantage of this new link. One researcher has transmitted information to colleagues in Israel and England so that the three can share research data and collaborate on a paper. Another found BITNET useful when he was arranging a conference for U.S. and Canadian scientists. He and the conference cochair at the University of Colorado found that using BITNET saved a lot of time when they were working on the administrative details of the gathering.

Applications such as these explain why computer networking is an advance receiving widespread attention. For scientists at NIH and around the world, networking is expected to open many new doors and accelerate the progress of research. ■


ADMINISTRATIVE WORKSTATIONS
LABORATORY WORKSTATIONS
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INTERFACE SOFTWARE
DATA BASE MANAGEMENT SYSTEMS
HIGH VOLUME BATCH
DATA ANALYSIS SOFTWARE
HIGH PERFORMANCE VECTOR/SCALAR PROCESSING
NIH LOCAL AREA NETWORK
NETWORKS OF LABORATORY WORKSTATIONS
NETWORKS OF ADMINISTRATIVE WORKSTATIONS
NETWORK OF CLINICAL WORKSTATIONS

At the center of this future plan for computing at NIH is DCRT's present central computer facility. The large central facility now supports a large community of users drawn from the laboratories, clinics, and administrative offices of NIH. It also communicates with peripheral computers in the scientific and management settings, and with offsite machines that are part of a larger national or international network. NIH PHOTO 2157

Editors of publications may request a glossy print of the numbered photographs appearing in this issue.

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DCRT programs focus on three prim-
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ding computer facilities.

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ıd clinical applications.

The **Laboratory of Applied Studies** relates mathematics, statistics, and computer sciences to such biomedical problems as ECG analysis, evaluation of physiological systems in health and disease, and estimation problems in laboratory medicine.

The **Laboratory of Statistical and Mathematical Methodology** provides statistical and mathematical help in the computer analysis of biomedical data and offers statistical and mathematical packages for users.

The **Physical Sciences Laboratory** conducts research in mathematical theory and practical instrumentation to explain biological phenomena in terms of chemistry and physics at the subcellular molecular levels.

The **Computer Center Branch** designs, implements, and operates the NIH Computer Center and provides assistance, training and technical communications to its nearly 17,000 users.

The **Data Management Branch** serves as a central systems analysis, design, and programming resource for data processing projects relating to scientific, technical, management, and administrative data.

The **Office of the Director** provides overall program and management direction for DCRT, and serves as the central NIH focus for automated data processing policy. It also provides guidance and support throughout NIH in the effective use of personal computer workstations and associated automation technology. In addition, the Office sponsors research and development work in molecular and cellular graphics.

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New Product Lessens Colic Symptoms 10

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About the cover:

At a recent workshop at NIH, researchers discussed a variety of health benefits that pets can provide to humans. The link between pets and human health is not a new one—but has only recently been methodically investigated. Workshop participants called for more targeted research into the benefits and risks of pets and into the mechanisms by which the human-pet bond influences health. See page **2**

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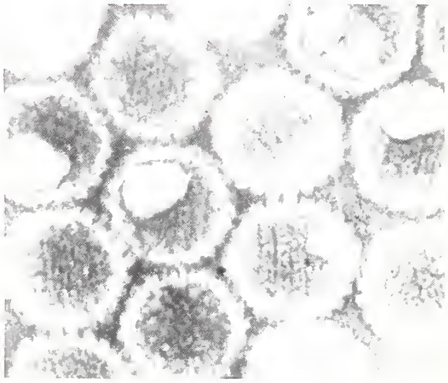
A recently conducted dental health survey shows that American adults are keeping their teeth longer. The survey found that only 4 percent of working Americans are toothless—a significant decline in recent years. Information from the survey, which included oral examinations on 21,000 adults ages 18-103, will be the basis for targeted research and education efforts by the National Institute of Dental Research (NIDR). See page **3**



A new test—developed by researchers supported by the National Institute of Allergy and Infectious Diseases (NIAID)—may diagnose herpes encephalitis (HSE) faster than brain biopsy. HSE is the most common cause of nonepidemic fatal encephalitis in this country—and quick, accurate diagnosis is crucial. The new monoclonal antibody test detects antigens of the virus that causes the disease and may assist physicians in selecting appropriate treatment sooner. See page **4**

NIH Workshop Focuses on Health Benefits of Pets

James Doherty

Pets in certain circumstances can provide health benefits to humans, researchers reported in a workshop September 10-11 at the National Institutes of Health (NIH) in Bethesda, Maryland.

Speakers at an NIH technology assessment workshop on "Health Benefits of Pets" pointed to a variety of benefits, including psychological improvements in depressed elderly people and lowered blood pressure in normal volunteers, but also said that research is needed to assess the clinical and long-term health significance of these findings. They recommend inclusion of pet therapy in established long-term health studies of the American population.

Some of the research results presented were:

- Looking at, talking to, and touching pets can temporarily reduce heart rate and blood pressure.
- Young children may turn to pets for comfort through touching and caressing, especially in families where both parents work or where moves are frequent.
- Pets may benefit depressed or bereaved elderly persons who have no other source of emotional support.
- Use of service dogs to help persons in wheelchairs tends to make social interactions easier and more relaxed both for the disabled person and for others.
- Therapeutic riding (also called "hippotherapy") has proved effective in helping certain people with a wide variety of problems, including multiple sclerosis, bedwetting, and lack of balance.

Speakers also discussed risks in contacts with animals, including bites, allergies, and tranmissible diseases. "But these risks are minimal with appropriate pet selection, planning, and training," said workshop coordinator Dr. Thomas Wolfle.

"Our task is to explore the scientific basis of the health benefits of pets and identify promising methods and research areas for the future," Dr. Wolfe said.

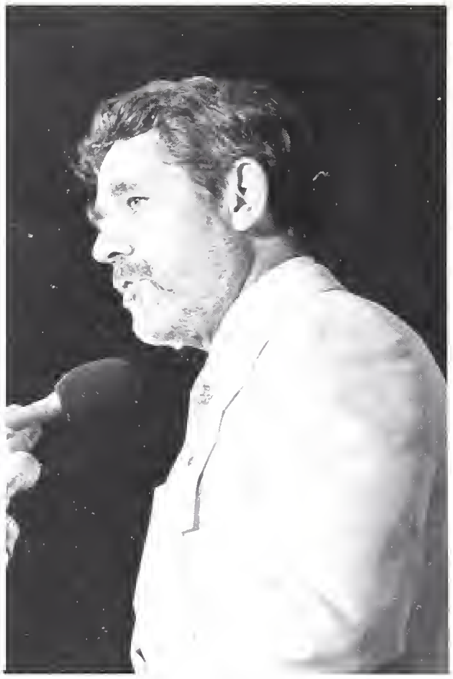
A link between animals and human health has been suspected throughout history, said Dr. Leo K. Bustad, former director of the People Pet Partnership Program at the Washington State University College of Veterinary Medicine. The role of animals in boosting the morale of sick and wounded soldiers has been recognized at least since the time of Florence Nightingale during the Crimean War of the 1850s, he said

Modern interest in pets as a part of therapy was sparked by clinical psychologist Dr. Boris Levinson at Yeshiva University in New York. Dr. Levinson discovered accidentally that having his pet dog present in the room during therapy sessions helped disturbed children communicate better. The methodological quality of research on health benefits of pets has been greatly strengthened during the 1980s, Dr. Wolfle said.

A summary statement prepared by the workshop's working group stated, "Future research in this area needs to assess the benefits and risks of the human/animal bond to both parties. Studies should clearly identify target populations and include healthy adults and children, senior adults, handicapped, and ill persons. These studies must identify mechanisms through which human-animal contacts influence health outcomes. We need to know more about the critical characteristics of people and animals to better ensure appropriate matches."

The two-day workshop was sponsored primarily by the NIH Division of Research Services and the Office of Medical Applications of Research. Other NIH sponsors were the Clinical Center, National Center for Nursing Research; National Heart, Lung, and Blood Institute; National Institute on Aging; and National Institute of Child Health and Human Development; as well as the Centers for Disease Control, and the Food and Drug Administration.

Additional information is available from the Office of Animal Care and Use, National Institutes of Health, Bethesda, MD 20892. ■



Dr. Thomas Wolfle, deputy director, Office of Animal Care and Use, Division of Research Services, answers questions from the press during a media conference held at the end of the two-day meeting.

NIH PHOTO 2170

Pets can offer benefits to many groups of people, especially the elderly.

NIH PHOTO 2171

NIDR Survey Reveals Significant Dental Health Improvements Among Americans

Susan Johnson

Quietly, almost unnoticed, modern dentistry has changed the face of America. The new American face has healthier teeth, and more of them, according to the results of a recent nationwide survey of dental health in American adults—conducted by the National Institute of Dental Research (NIDR).

Toothlessness has been almost eliminated in middle-aged adults, the survey revealed. Tooth decay is on the decline, at least in people under age 35. Americans visit their dentist regularly and enjoy a high level of dental care. "We can now look forward to a time, certainly within the next three to four decades, when no one need ever loose a tooth to disease," said Dr. Harald Löe, director of the NIDR.

Not that long ago, such a statement would have been unthinkable. In 1941, when the United States began drafting soldiers for World War II, dental defects were the leading cause of rejection for military service. Recruits needed at least six opposing teeth in each jaw—a requirement that many young men could not meet. To enlist enough men to fight for the U.S., the Selective Service had to eliminate virtually all dental standards.

Today, half of all working adults in the U.S. aged 18 to 64 have lost *at most* one tooth. Only 4 percent are toothless. This represents a significant drop in tooth loss not only since World War II, but even since a 1971-74 survey.

The evidence that people are keeping their teeth longer today comes from the National Survey of Oral Health in US. Employed Adults and Seniors, conducted by NIDR in 1985 and reported in 1987. The survey was the most comprehensive of its kind, and the first to look at the prevalence of root caries and periodontal disease in detail.

Over the course of a year, NIDR-trained dentists performed oral examinations on almost 21,000 adults aged 18 to 103. The exams were conducted at 800 business establishments and 200 senior centers located throughout the continental United States. The sample population—broken down into employed adults aged 18-64+ and nonemployed adults aged 65 and older—was selected to represent more than 100 million working adults and 4 million older Americans.

Toothlessness—in middle-aged adults—is almost a thing of the past, according to a national survey of dental health conducted by the National Institute of Dental Health (NIDR).

NIH PHOTO 2172

The survey showed that 37 percent of employed Americans had all 28 teeth (third molars, or wisdom teeth, were not included in this survey). Very few—only 4 percent—were toothless. Unfortunately, toothlessness remains a major problem among Americans aged 65 and older. Forty-one percent of the older people surveyed were missing all their teeth, and only 2 percent still had all 28 teeth.

Both younger and older adults continue to suffer from decay on the crowns of teeth, with a slightly higher rate in females than in males. Employed adults had an average of 23 decayed or filled coronal surfaces (out of 128 possible surfaces in people with all their teeth), and seniors had an average of 20. (Older people would be expected to have fewer, because they have fewer teeth left.) Almost 95 percent of the coronal lesions in both groups had been filled—an extraordinarily high level of dental care.

Decay of tooth roots was three times more extensive in seniors than in working adults. Normally tooth roots are protected below the gum line, but they can become exposed when gums recede over time or as a result of periodontal disease. Once exposed, they are vulnerable to decay. Root caries was found in 21 percent of the employed adults and 63 percent of the seniors surveyed. In both groups, only about half of the lesions had been filled. Root caries was more prevalent in men than in women, a reversal of the trend seen with coronal caries.

The majority of the adults surveyed showed signs of periodontal disease, with increasing prevalence and worsening of symptoms of age. Periodontal diseases destroy the supporting tissues that attach teeth to the jaw. Two measures were used to assess periodontal health: gums were gently probed at 28 sites to check for bleeding, which could be an early indicator of periodontal problems, and the sites were examined for loss of attachment of supporting tissues from the teeth.

Gingival bleeding was noted in 43 percent of the working adults and 47 percent of the seniors. Almost all of the people surveyed—84 percent of the employed group and 89 percent of the seniors—had tartar deposits on at least one tooth. Seventy-seven percent of the

One participant in the National Survey of Adult Dental Health receives his oral exam, while another waits her turn outside one of NIDR's mobile dental exam units.

NIH PHOTO 2173

working adults and 95 percent of the older group had at least one site in the mouth with periodontal attachment loss measuring 2 mm or more. Most severe periodontal destruction—attachment loss of 4 mm or more—was found in 24 percent of the employed adults and 68 percent of the older persons. Fewer than 8 percent of working adults and 34 percent of seniors surveyed had attachment loss of 6 mm or more. In both age groups, males had a higher rate of periodontal destruction than did females.

The survey also revealed that Americans are going to the dentist. Eighty percent of the employed adults and 76 percent of the seniors who still had teeth had visited a dentist within the past 2 years. Almost 60 percent of the employed group and half of the seniors said the main reason for their last visit was prevention and check-up. Only 29 percent of seniors with no teeth had seen a dentist in the past 2 years, and more than 70 percent said the main reason for their last visit was prosthodontics (branch of dentistry involving the replacement of missing teeth and other oral structures).

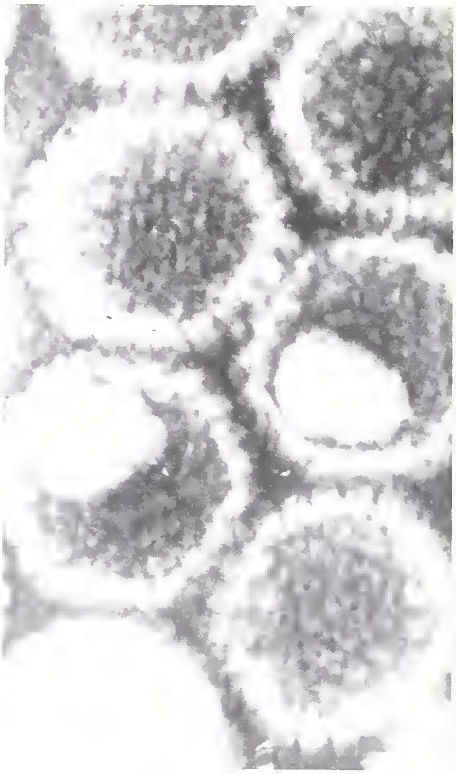
"The information from this survey will enable us to target our research and education efforts where they are needed most," NIDR's Dr Löe said, "Clearly, the worst problems are in the older segments of the population. This group has high rates of caries, periodontal disease, and tooth loss, with all the attendant pain and suffering, plus the need for dental services."

The overall picture from the survey, however, is one of continuing improvement in the oral health status of American adults, Dr. Löe said "We've compared our findings to those of surveys conducted in 1960-62, 1971-74, and 1981, and it's clear that people are keeping their teeth longer today. We can also see a drop in the rate of coronal caries over the past decade, at least in people under age 35."

With the adult survey results in hand, NIDR now has reliable data on the oral health of some 150 million Americans aged 5 to 85+. In 1980, the Institute conducted a national survey of dental health in schoolchildren. That survey revealed a dramatic drop in the rate of tooth decay over the previous decade. More than a third of the youngsters surveyed were caries-free, attesting to the effectiveness of fluoridation programs and improved oral hygiene practices. The prevalence of caries in the remaining children had been cut in half compared to a generation ago. A follow-up survey of oral health in schoolchildren is under way. ■

A New Antigen Test Helps Diagnosis of Herpes Encephalitis

Laurie K. Doepel



Electron micrograph of herpes simplex viruses without their viral envelopes. In extremely rare instances, herpes simplex virus 1, the same virus that causes cold sores in and around the mouth, travels along a nerve pathway or through the nose to the brain, causing a rapidly devastating brain infection known as herpes simplex encephalitis.

NIH PHOTO 2174

A new test—that may help diagnose a rare, but rapidly devastating viral brain infection, herpes encephalitis (HSE)—has been developed by researchers supported by the National Institute of Allergy and Infectious Diseases (NIAID) at the University of Alabama at Birmingham. Calling it "the most promising result of ten years of work," the team of scientists—Drs. Fred Lakeman, Junichi Koga, and Richard J. Whitley—has developed the first monoclonal antibody test to detect antigens (proteins that induce an immune response) of the virus that causes the disease.

Early treatment with the antiviral drug acyclovir reduces mortality and the risk of permanent brain damage. Unfortunately, physicians currently have no quick way to diagnose the disease. Most patients with presumed HSE now opt to start acyclovir treatment rather than wait to have the diagnosis confirmed by brain biopsy, which yields results in a few days. Consequently, an estimated 55 percent of suspected HSE cases turn out not to be HSE. While acyclovir will not harm those who do not have HSE, appropriate therapy for their diseases may be delayed.

The new test measures levels of herpes simplex virus 1 (HSV-1)—the cause of HSE—in cerebrospinal fluid (CSF). The spinal tap necessary to obtain CSF, a much safer and quicker procedure than brain biopsy, is already a part of the standard diagnostic exam for suspected HSE.

However, the researchers do not recommend that brain biopsy be supplanted by the antigen test until they improve its ability to detect early-stage disease.

The antigen test, though, gains accuracy the longer HSE has been present, and it can be used to distinguish HSE from other encephalitic diseases in later-stage cases. According to Dr. Whitley, patients with suspected HSE generally are cared for in local hospitals for as long as 7 to 8 days before being referred to a medical center where a brain biopsy can be performed. (Fewer than 50 medical centers in the United States are equipped to perform brain biopsies). "At the time our patients come in [for the antigen test]," says Dr. Whitley, "which is about the same time that patients come in for diagnosis by brain biopsy, the sensitivity and specificity of our test is beginning to match that of brain biopsy." Eight days after onset of symptoms, the antigen test's sensitivity (the proportion of those people with HSE correctly identified by the test) is 100 percent, and its specificity (the proportion of those people without HSE that the test indicates are disease-free) is 92 percent; these figures compare with the 96 percent sensitivity and 99 percent specificity of HSE brain biopsy. Additionally, results from the antigen test show up in 5 hours, whereas obtaining results from a brain biopsy usually requires 2 to 3 days.

Quick, accurate diagnosis of HSE is crucial; once settled in the brain, the virus works rapidly. HSE may not at first be suspected by patient or physician because the disease is rare and early symptoms—fever, lethargy, and head and muscle aches—mimic those of the flu. Within a few days, however, 40 percent of people with HSE experience seizures; some become disoriented or display personality changes. Often by day 6, a person with HSE will have partly or completely lost consciousness.

Left untreated, HSE has a 70 percent mortality rate. Antiviral drug treatment significantly decreases the chance of death, especially in younger patients. Treatment is less effective if instituted after a patient is comatose; 60 percent of such patients die, regardless of age, and treated comatose patients who survive are left with more serious brain damage than are non-comatose patients who receive treatment.

While HSE is a rare disease, the virus that causes it is a common one, causing cold sores in and around the mouth. About 90 percent of adults have been exposed to the HSV-1 virus.

When not causing active infection, HSV-1 lies dormant in the trigeminal ganglia, a group of nerves located on the side of the head. The trigeminal ganglia extends forward to the face and mouth and also in the opposite direction to the front and sides of the brain. The fact that HSE affects only these areas of the brain clued scientists that HSE probably results from a biological accident. Scientists theorize that in very rare instances the virus mistakenly travels from the trigeminal ganglia backward instead of forward, thereby ending up in the brain and causing HSE. The virus might also occasionally reach the brain after entering the nose.

Unlike the oral herpes virus, a genital herpes sore virus has no pathway to the brain and therefore cannot be implicated in HSE.

While the number of Americans affected by HSE each year is small, approximately 450 to 4,000 individuals, the disease is the most common cause of nonepidemic fatal encephalitis in the United States. Men and women are equally affected, but certain age groups—people below age 20 or above age 40—have higher incidences of the disease.

HSE may represent a first-time infection, a reinfection, or an activation of a latent infection. Younger people tend to have more primary infections, whereas older people display more reinfections or reactivations due to the gradual breakdown of immunity with age.

To detect HSV-1 antigen in their test, the investigators first dilute a very small amount of CSF and then dot blot it onto filter paper. The filter paper is incubated with a pooled solution of mouse monoclonal antibodies to four major antigens found on the surface of HSV-1-infected cells. A carrier molecule labeled with an indicator is then introduced into the system to detect any bound antibody.

Tests already exist to detect HSV-1 antibody levels within CSF. These tests, however, are less sensitive, less specific, and less accurate than the antigen test, and they also require more time and larger amounts of CSF. In addition, instituting antiviral therapy does not affect the measurement of HSV-1 antigen levels whereas it can skew the measurement of antibody levels.

The University of Alabama study was supported by the Collaborative Antiviral Study Group (CASG) program of the National Institute of Allergy and Infectious Diseases (NIAID). The goals of this program, a cooperative effort by scientists and physicians in 45 institutions nationwide, are to evaluate promising antiviral therapies, develop new diagnostic methods, and study the pathology and epidemiology of life-threatening human herpes virus infections. The CSF specimens used in the Alabama study came from 65 patients at CASG institutions who had undergone brain biopsy and were enrolled in clinical trials of potential HSE therapies.

Dr. Lakeman and colleagues are now awaiting corroboration of their results by a research group in Stockholm as they continue to try to refine the sensitivity of their test in early-stage disease.

This research was reported in a recent issue of the *Journal of Infectious Diseases.* ■

NCI Scientists Advance Understanding of Metastasis

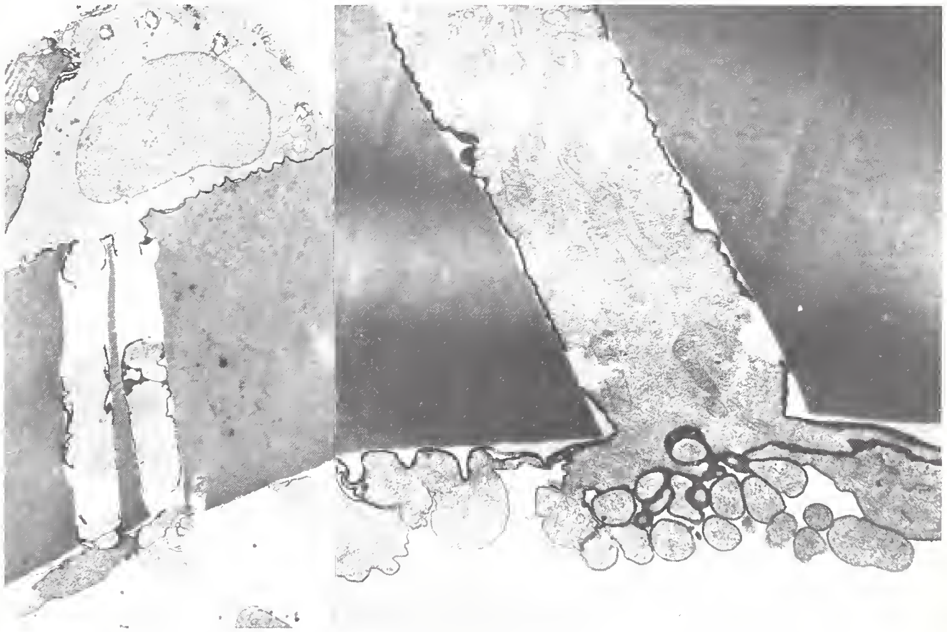
Cori Vanchieri

The future of pathology will be more than looking at tissue sections under a microscope, according to Dr. Lance Liotta, chief of the National Cancer Institute's (NCI) Laboratory of Pathology. He predicts that scientists will soon be able to test cells from the primary tumor and measure factors related to tumor aggressiveness, such as proteins, enzymes, RNA, and DNA. Based on these measurements, they will determine whether or not a tumor is likely to metastasize, or spread to other parts of the body. With this information, physicians will be better able to choose the most suitable treatment for each patient.

What had led Dr. Liotta to this forecast is his step-by-step unraveling of the process of cancer metastasis. "We need to understand metastasis, because failure to control it is usually what kills the cancer patient," he says.

In response to this need, researchers in Dr. Liotta's lab are trying to learn exactly how cancer cells cross tissue barriers to travel through the blood and lymph system to locations in the body beyond the primary one.

Their latest finding is that metastatic cancer cells produce a protein that causes them to extend sensors in the form of outreaching pseudopodia that enable them to migrate from the primary tumor site.



Left. From a vertical view, human breast cancer cell grown on filter sends pseudopodia through two adjacent pores of the filter. The pseudopodia were once continuous through the pore, but were broken during slicing for this electron microscopic photograph. (4,000X magnification)

Right. Magnified view of pseudopodium that extended through the filter and out the other side. (12,400X magnification)

Photos courtesy of Dr. Inger Margulies, NCI Laboratory of Pathology

NIH PHOTO 2175

In a recent issue of the British journal *Nature*, Drs. Raouf Guirguis and Elliott Schiffmann in Dr. Liotta's group describe the effect of this protein, called autocrine motility factor (AMF). When human breast cancer cells were exposed to AMF on a filter, they extended pseudopodia through the pores of the filter and began to migrate through the pores. With increased time and dosages of AMF, more pseudopodia developed.

"AMF has allowed us to show a keen relationship between pseudopodia protrusion and movement of the cell," says Dr. Liotta. The researchers have developed an anti-AMF antibody that inhibits pseudopodia protrusion, and, in turn, cell motility. This indicates that pseudopodia may be necessary for locomotion.

In addition to setting the cell in motion, the pseudopodia contain a number of receptors that act as the cancer cell's eyes, guiding it to its destination. One of the receptors binds to laminin, a protein of the basement membrane. This attachment to the basement membrane (a physical barrier that separates tissue compartments) is an integral step in the cell's journey. It must occur many times as the cells travel into and out of the circulatory system on their way to a secondary site.

Cancer cells bearing pseudopodia have a 20-fold increase in laminin receptors as compared with nonmetastatic cells. This increases their chances of attaching to the basement membrane. Laminin receptors are easily measured in tumor cells from patients with breast and colon cancer, and may prove useful as a predictor of the cancer's aggressiveness in individual patients.

Drs. Mark Sobel and Ulla Wewer in Dr. Liotta's group have cloned the gene for the laminin receptor. They have also designed two substances that can recognize the receptor and inhibit human tumor cells from binding with laminin. One is a synthetic fragment of laminin and the other is a monoclonal antibody to the receptor. Dr. Liotta and others have shown that the fragment and the antibody can stop metastatic spread of melanoma, or skin cancer, in mice. Clinical trials in humans are planned to determine whether the fragment or the antibody coupled with toxins can locate and destroy the metastatic cancer cells.

Once metastatic cells attach to the basement membrane, they have to break through it. That occurs with the help of an enzyme produced by the invading cells, called Type IV collagenase.

"There is a strict correlation between the collagenase and metastasis in many experimental systems," Dr. Liotta says. Measurement of this enzyme may be another way to predict tumor aggressiveness.

Looking into the genetic control of metastasis, Dr. Ruth Muschel and coworkers in Dr. Liotta's lab have pinpointed a gene that can cause cells to become highly metastatic. It is called the *ras* oncogene. It activates other genes that produce the proteins and enzymes (including collagenase) that cause locomotion via pseudopodia, followed by attachment to and penetration through the basement membrane. The researchers are working on ways to measure alterations in the genes of human tumor cells.

Through all these efforts, NCI's Laboratory of Pathology is moving closer to providing better treatment through improved diagnosis of cancer's metastatic potential. ■

Nationwide Study Reveals New Findings on Latchkey Children

Tineke Boddé Haase

The "latchkey" phenomenon—children who care for themselves after school—is less widespread than is commonly believed, and most latchkey children are white, older (10-13 years), and from suburban and rural areas. They are also from wealthier, better-educated families for whom self-care seems to be a choice rather than a last resort. These are the findings of a team of demographers from the National Institute of Child Health and Human Development (NICHD) who studied 60,000 American households involving 20,000 children ages 5 through 13.

Drs. Virginia Cain and Sandra Hofferth of NICHD's Center for Population Research found that 2.1 million or 7 percent of U.S. children aged five through 13 are not supervised by an adult after school. A total of approximately 2.4 million children are in self-care before school, after school or at night, or are in the care of someone under age 14. These data contradict earlier reports which estimated that as many as 7 to 15 million children are unsupervised after school.

As part of their research to study the impact of family changes (divorce, single parenthood, and maternal employment) on the care of school-age children, Drs. Hofferth and Cain added several questions to a 1984 Bureau of Census population survey to determine how many children regularly spent any time alone or in the care of someone under age 14. The questions were asked in a neutral way to avoid underreporting.

The findings include:

- Most "latchkey children" are unattended for at most two hours a day. Many of these may be in telephone contact with a parent during that time.

- Self-care is no more prevalent among children from single-parent than 2-parent families.

- Children with many siblings are more likely to be in self-care (which includes care by a sibling under age 14) than children with fewer siblings. However, children in families with more adults that just parents (e.g. grandparents) are less likely to be in self-care.

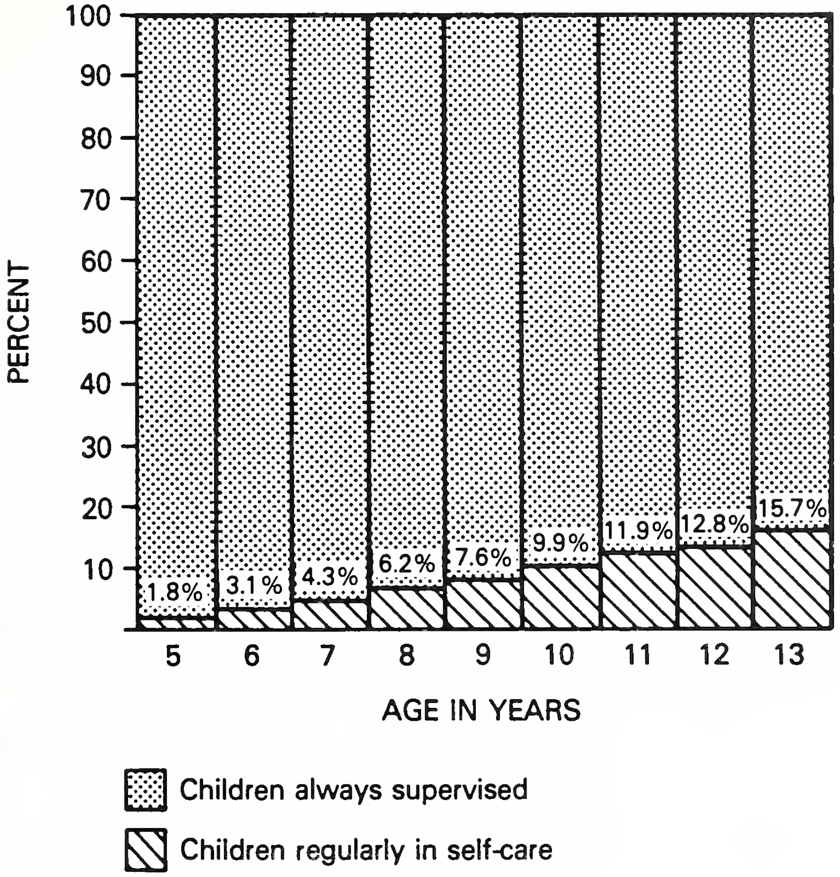
- Employment of the mother per se has no consistent positive or negative impact on the decision to use self-care for the child.

- Although most latchkey children are older, middle class children, a small number of self-care children may be at extreme risk. For example, an estimated 231,000 5- to 7-year-olds are in self- or sibling care after school, and 32,000 of these are left alone or with a sibling for three or more hours.

"This study puts the entire latchkey phenomenon in a better perspective," says Dr. Hofferth. "Although we occasionally hear horror stories about very young children caring for themselves when their parents work, such stories are unusual. We know now that fewer than 2 percent of 5-year-olds care for themselves while their parent(s) work" (See chart).

Nevertheless, Drs. Cain and Hofferth believe there is a reason for concern. "The number of school-age children whose mothers work outside the home has increased dramatically in the past 15 years and will grow even more," Dr. Hofferth says. "If current trends continue, three-fourths of all school-age children and two-thirds of preschool children will have mothers in the work force by 1995, according to the Bureau of the Census. That means that eight years from now, the number of school-age children with an employed mother will reach 34.4 million, which is 37 percent more than in 1980 and 34 percent more than in 1985," Dr. Hofferth says. As a result, there will be increased demand for infant care, before-and-after school programs, and instruction of youngsters in self-care techniques.

CHILDREN REGULARLY CARING FOR SELF OR IN CARE OF OTHER CHILD UNDER AGE 14



Most latchkey children are 10 years or older. Based on a study of 60,000 households involving 20,000 children, NICHD demographers estimate that 2.4 million children ages 5 through 13 years are regularly caring for themselves or are placed in the care of another child under age 14. Approximately 1.8 percent of the 5-year-olds, and 15.7 percent of the 13-year-olds are regularly in self-care.

Source: 1984 Current Population Survey

NIH PHOTO 2176

Self-care of children, too, is likely to increase. The psychological impact of self-care on children has been the source of much controversy. "Some researchers have found that self-care children are more lonely and fearful and are more likely to engage in deviant behavior than do supervised youngsters," Dr. Cain says. "Other studies show no negative effects of self-care on the child's social and psychological functioning. It appears that the activities of the child while in self-care, and the level of parental supervision in absentia may be important for the outcome of self-care. In addition, parents may simply be more willing to leave independent, mature children in self-care," Dr. Cain said.

The researchers conclude that "without knowing the characteristics of latchkey children as a group, it is difficult to assess the impact of self-care on children. This nationwide study is a valuable first step. It can be used as a baseline for future research on how different types of self-care and after school care affect a child's social and emotional development." ■

NIGMS Researchers Study Protein that May Assist Recovery from Injury

Doris Brody

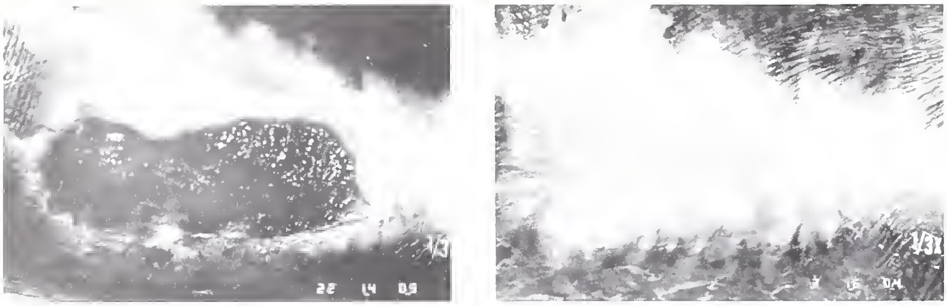
Wound healing and the body's response to trauma are extremely complex processes that involve a host of specialized cells and protein molecules. Many researchers are studying these processes by examining their individual components, and are beginning to identify certain factors that may yield useful treatments for trauma patients and wound healing. Improving the body's ability to recover from injury is especially important for patients with infections, severe injuries, or certain diseases, such as diabetes, that impair healing.

The National Institute of General Medical Sciences (NIGMS) is supporting two scientists—Frederick L. Grinnell, Ph.D. of the University of Texas Health Science Center at Dallas and Thomas M. Saba, Ph.D., of Albany Medical College of Union University in Albany, New York—whose studies of wound healing and recovery of organ function after trauma are focusing on the protein fibronectin. Although much remains to be learned about fibronectin, reseachers are beginning to believe it can be used to treat patients with slow-healing wounds and infections.

Fibronection occurs in two biochemically similar forms, plasma and tissue. Plasma fibronectin, which is soluble and found in body fluids, helps the body get rid of certain types of debris, including that which accumulates as a result of injury.

Tissue fibronectin is a vital component of the extracellular matrix—the loose association of organic molecules that helps bind cells together to form tissues. In this matrix, fibronectin molecules act as a biological adhesive by connecting cells with the other protein components of tissue. Fibronectin molecules also form pathways for migrating cells, including those essential for wound repair.

Cancer researchers were the first to discover fibronectin's role in cell organization when they noticed that, unlike normal cells, the surfaces of tumor cells often lack the protein. Since cultured tumor cells do not adhere well to a plastic substrate, the researchers speculated that this might be due to the absence of fibronectin. When they added fibronectin, the cells' adhesion improved. The additional fibronectin also permitted



Before and after photos of a leg wound show dramatic results in healing using fibronectin.

Photos courtesy of Annette B. Wysocki, Ph.D., The University of Texas Health Science Center at Dallas NIH PHOTO 2177

the intracellular matrix of protein filaments, which is very disordered in cancer cells, to return to normal. Unfortunately, however, the tumor cells continued to multiply rapidly.

Dr. Grinnell has been studying the basic mechanisms by which new tissue forms to heal wounds. He has learned that fibronectin promotes migration of the skin cells that close wounds. An offshoot of this work has led to the experimental use of eye drops containing fibronectin to improve healing of corneal ulcers.

More recently, Dr. Grinnell and his coworkers have been studying fibronectin as a possible treatment for chronic ulcers. Nonhealing ulcers, usually of the arms and legs, are a serious health problem. For instance, according to a U.S. Public Health Service study, 128,000 patients were hospitalized in 1979 for this kind of wound for an average length of 11.4 days each. At $200 a day, this would have cost nearly $300 million.

In preliminary studies, the researchers found that a patient treated with topical applications of fibronectin experienced a 90 percent reduction in the size of a leg ulcer that had been treated unsuccessfully for 5 years by the most advanced experimental as well as conventional therapies. The research will continue in order to compare this dramatic result with the responses of additional patients.

Dr. Saba and his colleagues are studying multiple organ failure associated with infection in surgical, trauma, and burn patients. Organ failure, especially lung failure (a condition known as ARDS, or adult respiratory distress syndrome), is a frequent cause of death in trauma and burn patients. Preliminary studies by this group of researchers indicated improvements in organ and certain immune system functions following fibronectin-rich infusions in trauma patients with severe infections.

Since Dr. Saba and his colleagues suspected that fibronectin was the component of the infusions that was responsible for the improvement, they recently initiated a study in which they infused patients with pure plasma fibronectin. This study was conducted primarily to detect any short-term abnormal response to the fibronectin itself and was not designed to examine the effects of the protein on organ function. None of the six patients studied showed any abnormal reaction to the fibronection infusion.

The patients in the study also showed an improvement in certain immune system functions, similiar to that found in the earlier research using fibronectin-rich material. The scientists believe this improved biological activity will help in the removal of debris from the blood, which should minimize lung injury and thus prevent ARDS. Dr. Saba notes, however, that further clinical trials need to be conducted before the value of fibronectin in treating post-surgical or burn- and trauma-related infections can be fully evaluated. ■

NHLBI Study of Cold-Blooded Animals Unlocks Secret for Improving Safety of Heart Surgery

Karen Perkins

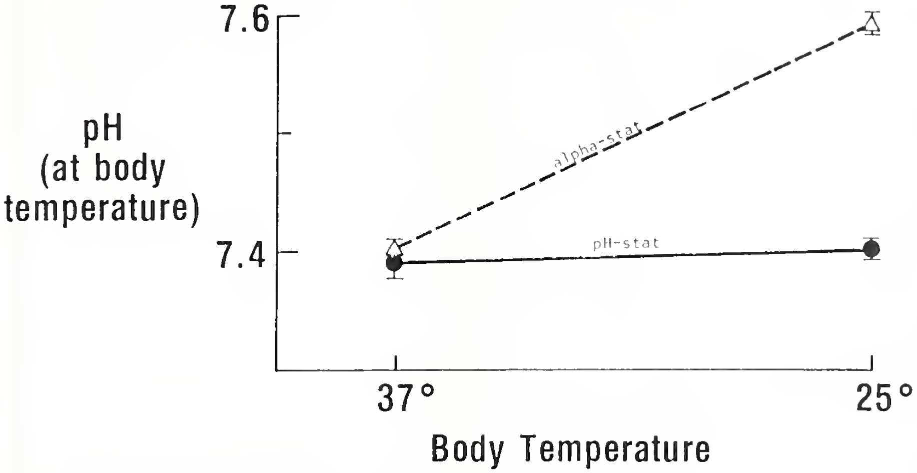
Every year some 200,000 Americans must undergo coronary artery bypass surgery, a technique that involves bypassing one or more narrowed or blocked coronary arteries (usually with venous segments taken from the leg) to restore adequate blood flow to areas of the heart. To perform this surgery, physicians use a device called the heart-lung machine to take over the functions of the heart and lungs while the heart is stopped.

Since its introduction in the 1950's, major strides have been made in improving the safety of this strategy, called cardiopulmonary bypass. But because cardiopulmonary bypass usually involves hypothermia, or lowering the body temperature, to decrease the body's need for oxygen, questions have been raised about how best to manage a patient in this cooled state. Of particular concern is acid-base homeostasis, since acid-base disturbances can endanger the electrical stability of the heart and create life-threatening situations.

To better understand the conditions that accompany hypothermia, scientists have been studying cold-blooded or ectothermic animals, such as turtles. Unlike humans, these animals normally experience a wide range of body temperatures that vary with the temperature of the surrounding environment. As their body temperature falls, the pH (a measurement of the acid-base status) of their blood and tissues rises.

One of those scientists is National Heart, Lung, and Blood Institute (NHLBI) cardiac surgeon Dr. Julie Swain, who has been conducting research aimed at improving the safety of bypass surgery by investigating the changes that occur metabolically when various acid-base management schemes are used.

"There are two ways to manage pH that are used clinically," says Dr. Swain. Traditionally, the strategy of most cardiac surgeons has been to maintain pH at 7.4, the "normal" level for people and other warm-blooded animals—a strategy called pH-stat. A newer, and possibly safer, method is called alpha-stat, in which surgeons allow pH to rise as temperature falls (see diagram). "That is how cold-blooded animals manage pH, and that is



By following the ectothermic scheme (pH rises as temperature falls), the alpha-stat method of pH management during hypothermia may be a safer way to conduct cardiopulmonary bypass surgery than the traditional pH-stat method.

NIH PHOTO 2178

what we are investigating at the NIH both in the animal laboratory and in the operating room." She adds, "Half of the surgeons in the country use the alpha-stat method now, but many questions still are not answered about what is the best method and why."

Before working with the NHLBI, Dr. Swain was doing research in hypothermia at the Scripps Institution of Oceanography of the University of California at San Diego. She worked with Dr. Fred White, an expert in comparative physiology and director of the Institution's physiology laboratories. There, she realized that the knowledge of comparative physiologists, who encounter hypothermia in cold-blooded animals, could provide valuable insights into the management of patients during cardiac surgery. "We thought we could learn something about how to manage man by how animals manage hypothermia," says Dr. Swain.

Scientists have been studying cold-blooded animals, such as the turtle, to understand how the body responds to hypothermia.

Photo courtesy of Francie Schroeder, National Zoological Park

NIH PHOTO 2179

Although the main aim of her research is to improve the safety of cardiopulmonary bypass, an improved method of pH management would also play a vital role in treating people who accidentally experience a dangerous drop in body temperature. Such accidental hypothermia victims are in danger of ventricular fibrillation, a distorted rhythm of the heart that leads to death. Dr. Swain has shown that when the alpha-stat scheme is used while carefully rewarming these victims, the heart is more electrically stable and can be more easily prevented from fibrillating.

Alpha-stat promises to assume increased importance in open heart surgery, especially for those patients who are in the poorest medical condition. "For those borderline patients," says Dr. Swain, "it may make the difference between pulling them through or not." ■

NIDR Researchers Report Taste Unimpaired in the Absence of Saliva

Jody Dove

Saliva is commonly thought to be critical in maintaining the function of taste cells. Recently, however, researchers from the National Institute of Dental Research (NIDR) found that taste cells may continue to function normally despite a chronic absence of saliva.

In a study published in *The Proceedings of the National Academy of Science* Drs. James Weiffenbach, Philip Fox, and Bruce Baum of the NIDR Clinical Investigations and Patient Care Branch described eight female patients whose ability to taste was normal despite an absence of salivary gland function.

The absence of salivary function in the patients was confirmed by objective measures, such as flow rate, biopsy, and salivary gland uptake of radioactive tracer. Taste perception was assessed by subjective reports and by objective measures of threshold and suprathreshold sensitivity. Threshold sensitivity reflects the weakest concentration of a taste solution that a patient reliably discriminates from distilled water. Suprathreshold tests, in contrast, use clearly detectable stimuli to assess the perception of taste intensity. The four basic taste qualities—sweet, sour, salty, and bitter—were represented by essentially odorless solutions of sucrose, sodium chloride, citric acid, and quinine sulfate.

The NIDR investigators compared the eight patients' responses to each taste test with those of normal volunteers participating in the National Institute on Aging's (NIA) Baltimore Longitudinal Study of Aging. Taste perception among the eight patients was notably unimpaired. One patient, for example, not only reported no taste complaints, but also denied alterations in taste sensitivity and performed within normal limits on every test for all taste qualities.

As a group, the eight patients were no more frequently impaired on objective measures of intensity perception than were the normal volunteers. Even though their threshold performances were impaired somewhat more often than those of normal people, it is clear that salivary gland failure does not necessarily lead to loss of taste function.

The researchers suggest that future studies, rather than focusing on salivary components thought to be responsible for the functional integrity of taste cells, should focus on the taste cells themselves. ■

NIEHS Scientists Study Environmental Estrogens and Their Impact on Health

Hugh James Lee

When is an estrogen not an estrogen? The answer to this scientific riddle has fascinated researchers at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, N.C. for fifteen years. The answer seems to be that estrogenic activity in the human body may be prompted, or, in some cases, inhibited by a number of chemicals that gain entrance by being ingested, inhaled, absorbed by the skin, or enter the body in other ways, some perhaps not yet known. These chemicals may be in the form of additives to livestock feed ultimately eaten by us in meat, as pharmaceuticals, recreational drugs, or as organic forms in nearly all the plant products we eat.

In other words, the estrogens produced in women's bodies, and to a lesser degree in men's, are mimicked by a wide array of synthetic and natural chemicals. Clearly, most of these don't disrupt human health or the ability to conceive and deliver healthy offspring. Yet, a few of them do, and some may exert subtle influences that create problems in the long run or affect the future of fetuses exposed to them through their mother's bodies.

John A. McLachlan, Ph.D., chief of the Laboratory of Reproductive and Developmental Toxicology at NIEHS, has been studying the many faces of estrogens in the environment for much of his adult life. In seminar presentations he projects a slide showing perhaps two dozen molecular diagrams of chemicals that have demonstrated estrogenic activity and notes that twenty plant estrogens, or phytoestrogens, have been identified in 300 species of plants, and that many synthetic chemicals show estrogenic activity.

Normal estrogen production and activity in the body serves a number of known functions. Its production signals the changes that transform a girl into a woman at puberty, and it is among the hormones that controls the menstruation cycle and plays a critical role in events of pregnancy and birth. While less central in the male system, estrogens are present, and heavy exposure to environmental estrogens has been seen to cause health problems, breast enlargement in a young boy who took estrogen contaminated vitamins, for example, and loss of libido and sterility in adult men occupationally exposed to chlordecone, a pesticide with estrogenic activity.

Dr. McLachlan, in collaboration with his colleague of 15 years, Retha Newbold, authored some of what are now the textbook studies of the effects of the synthetic estrogen diethylstilbestrol, or DES, a hormone widely administered to pregnant women during the early 1960's to prevent miscarriages. Using mice as surrogates to find out more about the effects of DES on reproduction, Dr. McLachlan found that the female offspring of DES-treated mice developed the same reproductive tract malformations and vaginal cancers that were being detected in some human daughters of DES mothers. From the mouse model, he also predicted reproductive tract defects in males, which were later observed in some human DES sons.

Such human health effects are often extremely difficult to track down. Currently, Dr. McLachlan is among those involved with hunting the source of estrogens that may be involved in reports of very young children in Puerto Rico with premature sexual development, which is manifested as breast development in two year olds and menstruation in girls of three. Diet is one of the first suspects, although investigators have not yet identified the source.

Diet is the route of exposure for another environmental estrogen that causes sterility and liver disease in big cats kept in zoos. It has been noticed that certain large wild cats in zoos in some Western countries cannot produce offspring. This, in turn, has been linked to the high estrogen levels produced by soybean products added to their diets that act like estrogen-containing birth control pills used by women. With the soy left out of their diets, the estrogen levels in collected urine samples decrease, but researchers are waiting to see if this will result in pregnancies.

NIEHS scientist, Donna Baird, Ph.D., of the Division of Biometry and Risk Assessment, will investigate yet another approach to dietary plant estrogens, measuring the estrogen levels in postmenopausal women volunteers who go on a high soy content diet. Since this population group suffers from several health complaints resulting from low estrogen, such as loss of bone mass, researchers will look at a possible positive effect of environmental estrogens by determining if the soy diet raises estrogen levels.

NIEHS has already sponsored two major international conferences on estrogens in the environment in 1979 and 1984, and plans another in 1989. By bringing together scientists and physicians from throughout the world, researchers will be better able to confront this complex subject through a free exchange of information.

Wild cats, soybeans, mice and people—research on estrogen in the environment boldly illustrates how different forms of life within the environment are interrelated and illustrates the fact that plants and even synthetic chemicals can "speak the same chemical language" as the specialized chemicals called hormones that are naturally produced within our bodies. By better understanding these relationships, scientists at NIEHS contribute to knowledge that can assure better health for us and for future generations. ■

NICHD Study Shows that New Product Eases Colic Symptoms in Infants

James Hadley

For years physicians and scientists have not known what causes colic or how to treat it effectively. While the cause or cure has not yet been found, a new product called SleepTight, which stimulates the motion of a car ride, has been shown to lessen colic symptoms in 58 out of the 60 infants tested during the 3-year Infant Colic Research Project, supported by the National Institute of Child Health and Human Development (NICHD). The study also found that 85 percent of the babies stopped crying within 4 minutes of using SleepTight.

This is welcome news to parents who cope with colicky babies. Although there are no firm statistics on the number of infants affected by colic, physicians estimate that 9 to 23 percent of infants up to 3 months of age experience colic.

Babies with colic are irritable and fussy and tend to cry or scream intensely. This is accompanied by body spasms and tensions. The symptoms usually start after a baby's meal in the late afternoon or evening, disrupting the child's normal eating and sleeping habits. Typically, colic persists for 10 to 12 weeks. It starts as early as 2 to 3 weeks of age and ends—sometimes as abruptly as it started—around 12 weeks.

SleepTight, a patented medical device, consists of a vibration unit and a sound unit that simulate a car ride at 55 miles per hour. Mounted underneath the crib, the 3.5 lb. vibration unit gently rocks the crib while the other unit, attached to the side of the bed, provides the rushing sound of wind passing a closed car window.

SleepTight, a patented medical device, consists of a vibration unit and a sound unit that simulate a car ride at 55 miles per hour. Mounted underneath the crib, the 3.5 lb. vibration unit gently rocks the crib, while the other unit, attached to the side of the bed, provides the rushing sound of wind passing a closed car window.

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The idea for the device came from a desperate parent. Armando Cuervo began work on this project 5 years ago after his own son, Andrew, had colic and kept Cuervo and his family awake for hours on end.

"This was the worst experience I have ever had in my life," says Cuervo. "One night at 2:30 in the morning I decided I couldn't take it anymore. I called the doctor and told him what was happening. I needed help! I told him to do something about this child. He agreed to meet me and the baby at his office."

A strange thing happened on the way to the doctor. Cuervo noticed his son's crying began to decrease. By the time they arrived at the doctor's office the baby was sound asleep.

Thus, the idea was born to make a device that would recreate that car ride. After consulting with several experts, Cuervo designed SleepTight. Cuervo, who has a bachelor's degree in chemistry and a master's in business administration from Washington University in St. Louis, sought funds from the NICHD to test scientifically the effectiveness of the product and, if possible, improve its design and performance.

Armando Cuervo with son Andrew, who as an infant suffered from colic and spurred his father to invent SleepTight. The patented medical device simulates the motion of a car ride, which gently rocks the crib, while the unit Andrew is holding provides the sound of wind.

NIH PHOTO 2181

"NICHD is particularly proud of this accomplishment because it is the first product under its Small Business Innovation Research (SBIR) Grants program to be marketed directly to the public for use. Other devices or services invented or funded under the program have mainly aided scientists in their research," said Dr. Duane Alexander, NICHD director.

For more information, write Sleeptight at 3613 Mueller Road, St. Charles, Missouri 63301 or call 1-800-325-3550. ■

Plastic Flow Model System Developed to Improve Drug Delivery

James Doherty

Engineers in the Biomedical Engineering and Instrumentation Branch (BEIB), Division of Research Services (DRS), are using transparent plastic models of human arteries to solve problems relating to drug delivery via the blood stream.

Dr. Robert Lutz, Mr. John Boretos, and coworkers in BEIB's Chemical Engineering Section have developed a sophisticated *in vitro* model system to mimic and visualize the flow of blood and infused drugs in the carotid artery and its major branches. Pumps and a series of flow resistors and flow capacitators permit the engineers to vary conditions at will. They have also developed a flow model of arteries in the liver.

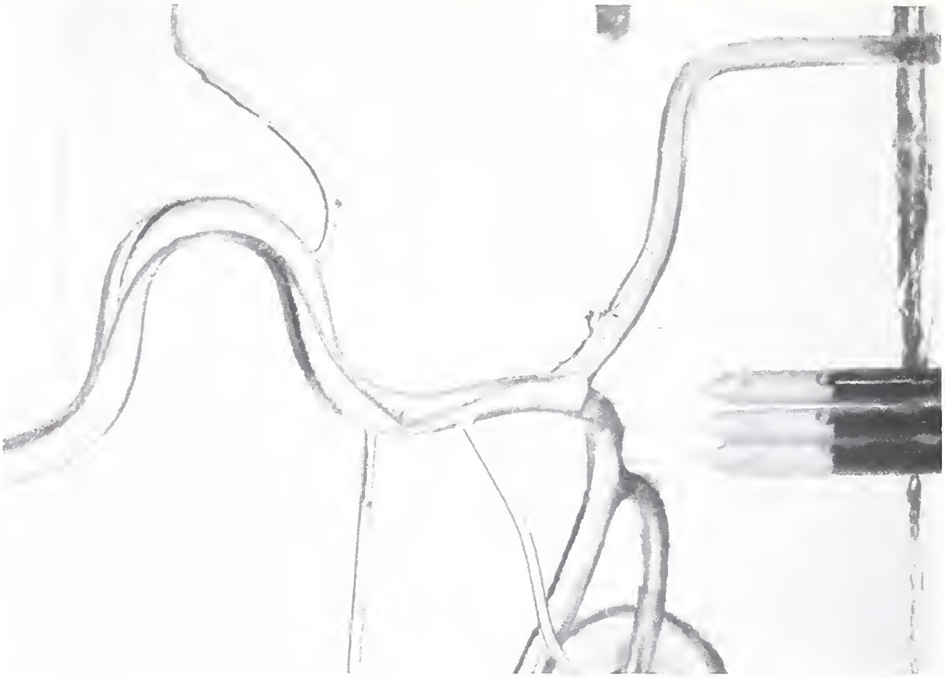
The BEIB models show what happens when a drug solution leaves the tip of a catheter located within a blood vessel. A dye represents the drug solution, and a glycerin-water solution represents the blood. In some situations, the drug solution remains in a separate stream instead of mixing with the blood as desired.

Scientists at several research institutions have reported sporadic cases of retinal damage and localized brain toxicity following clinical trials when chemotherapeutic agents for brain tumors were infused through an artery. Dr. Lutz and his collaborators developed the flow model to test whether inadequate solutions leaving a catheter tip can cause these toxicities.

They studied the flow of dye solutions at varying infusion rates and with several types of catheters at various positions. They recorded the visual results on videotape and film, collected samples of the streams from the arterial branches, and used spectrophotometry (process for measuring the quantity of matter in solution by measuring the quantity of light absorbed) to determine the relative concentrations of dye in each branch.

The studies revealed that at the commonly used infusion rates of 2 to 4 milliliters per minute, the drug solutions emerge in stable streams that may distribute the drug nonuniformly in the branches. This may cause toxic concentrations of drug in some tissue regions and subtherapeutic levels in others.

The carotid and the liver flow models are being used to test catheter designs and to develop better drug delivery methods, including faster infusion rates to allow for better mixing of drugs with blood.



In a BEIB plastic carotid flow model, dye from a catheter, streaming through a glycerin-water solution, illustrates inadequate mixing of infused drug solution with arterial blood

NIH PHOTO 2182

BEIB engineers and physical scientists have long been collaborating with Drs. John Doppman, Edward Oldfield, and Donald Miller and with other investigators in the NIH Clinical Center (CC), the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the National Cancer Institute (NCI) on projects to safely increase the concentrations of chemotherapeutic drugs delivered to the site of tumors. Related projects include several types of miniature catheters that can enter previously inaccessible small blood vessels and a system that filters chemotherapeutic agents from the circulatory system after the drugs have passed the tumor area.

Dr. Lutz has also undertaken a different use of the flow models in collaboration with Judith L. Collins, R.N., of the CC Cancer Nursing Service; studies of what happens when two incompatible drugs are infused from separate lumens of one catheter. In clinical care, it often becomes necessary to infuse multiple drugs into a patient because of complex care needs and poor access to veins. If these drugs interact in solution, one or the other may precipitate or become inactive. Multilumen catheters are commonly used to keep these incompatible drugs separate in the blood stream. Studies in *in vitro* flow systems are being conducted to document the safety and efficacy of this method.

Dr. Lutz states that *in vitro* systems, such as the flow model, reduce the number of animals needed for experimentation. In addition, the flow models provide data not readily attainable *in vivo*. ■

RESEARCH HIGHLIGHTS

The following items are research highlights from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)—the newest of the NIH institutes. The NIAMS, established in 1986, leads a national program in arthritis and musculoskeletal and skin diseases, which was formerly under the direction of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK). NIAMS provides support for basic and clinical research and research training on the causes, prevention, diagnosis, and treatment of a large number of diverse diseases, including rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, osteoporosis, Paget's disease, epidermolysis bullosa, and many others.

New Genetic Marker Found for Ankylosing Spondylitis

NIAMS-supported researchers, John Reveille, M.D., and associates at the University of Alabama, Birmingham, and in Portland, Maine, have identified a genetic factor that strongly predicts the development of ankylosing spondylitis, a form of spinal arthritis.

Although the cause of ankylosing spondylitis is unknown, researchers had previously discovered a strong genetic marker, HLA-B27, in 90 percent of patients with the disease. This factor is found in 6 to 8 percent of the white population, although a much smaller percentage of the white population develops ankylosing spondylitis.

In order to determine if there are other factors that might interact with HLA-B27 in determining susceptibility to the disease, the researchers studied 6 families comprising 48 individuals, in which 11 members had ankylosing spondylitis. Each family member was evaluated for the presence of a specific DNA fragment (RFLP) as well as for the HLA-B27 factor. They found that all 11 family members with ankylosing spondylitis had both the HLA-B27 factor and the RFLP. In a separate study, the researchers determined that the HLA-B27 factor and the RFLP were inherited independently of each other.

The scientists said that this new data represents the first successful demonstration that the RFLP, together with the HLA-B27 factor, confers a high risk for developing the disease. According to Dr. Reveille, "Our studies show that an individual who has both the genetic marker HLA-B27 and the RFLP has almost 300 times greater risk of developing ankylosing spondylitis as the person who has neither."

Ankylosing spondylitis is a type of arthritis that affects the spine and occurs mainly in young white males between the ages of 16 and 35. According to the Ankylosing Spondylitis Association, approximately 2.5 million Americans may have the disease.

These results were published in a recent issue of *Arthritis and Rheumatism.* ■

Barbara Weldon

Environmental Factor May Trigger Autoimmune Skin Disease

A skin disease in which the body attacks its own tissue may be triggered by an environmental factor, according to a study that examined 10,000 cases of the disease reported since the 1940's. The disease is a form of pemphigus, a serious skin disorder in which severe blistering and skin erosion occurs.

NIAMS-supported researcher Luis A. Diaz, M.D., professor of dermatology at the Johns Hopkins Medical Institutions in Baltimore, found that more than 90 percent of cases occurred in persons living in rural, central areas of Brazil that are heavily infested with a species of blackfly. In these infested areas, the disease, known as Brazilian pemphigus foliaceus (Fogo Selvagem - FS), is common and endemic. Dr. Diaz, working with Brazilian researchers at the University of Sao Paulo, has implicated the blackfly as a possible carrier of a substance that triggers the disease.

"If a substance were found," Dr. Diaz said, "this would be the first human autoimmune disease where an external cause has been determined. Such a discovery may provide insights into the development of other autoimmune diseases, such as lupus erythematosus and rheumatoid arthritis."

Autoimmune diseases result from the body's production of antibodies (called autoantibodies) that attack the patient's own tissues. In pemphigus foliaceus, the skin is the target of attack, which causes it to blister and erode. Once considered a fatal disease, pemphigus foliaceus now can be controlled with corticosteriods. According to the research team's analysis, this blistering disease occurs more frequently in related family members, so a genetic predisposition for the disease appears to exist.

To confirm his epidemiological findings, Dr. Diaz has received additional funding from the NIAMS and the NIH Fogarty International Center (FIC) to begin a prospective study of patients with pemphigus foliaceus and to conduct in-depth studies on agents in the blackfly that may activate the disease in susceptible people. ■

Patricia Blessing

Similarity Found Between Joint Tissue in Lyme Disease and Rheumatoid Arthritis

NIAMS-supported scientists Allen Steere, M.D., and associates at Yale University, New Haven, Connecticut, and Stanford University in California have found a remarkable similarity between the synovium (joint lining) of patients with Lyme disease and that of patients who have rheumatoid arthritis.

In Lyme disease, a major feature is chronic joint inflammation resembling rheumatoid arthritis. Since Lyme disease was first identified in 1975 by Dr. Steere, it has been found in thousands of people along the Atlantic coast and in some Midwestern and Western states. The disease is now known to be caused by a tick-borne spirochete (a spiral-shaped bacterium).

Rheumotoid arthritis is a chronic inflammatory disease of unknown cause. Its major symptom is swollen, painful joints. As many as 7 million Americans have been estimated to have the disease.

Dr. Steere's group studied synovial samples from 12 patients with Lyme disease and 12 with rheumatoid arthritis. The appearance of the synovial lesions from both sets of patients was nearly identical. In addition, the researchers found that in six of the patients with Lyme disease, a few spirochetes were seen in and around the blood vessels in the synovial lesion. The researchers believe, therefore, that the stimulus for chronic joint inflammation in Lyme disease is likely to be a small number of live spirochetes that persist in the joint tissue for years.

According to Dr. Steere, "These findings give greater credibility to the idea that infectious agents may be responsible not only for Lyme disease, but also for rheumatoid arthritis and may actually be present in the joint tissue." ■

Barbara Weldon

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November 1987

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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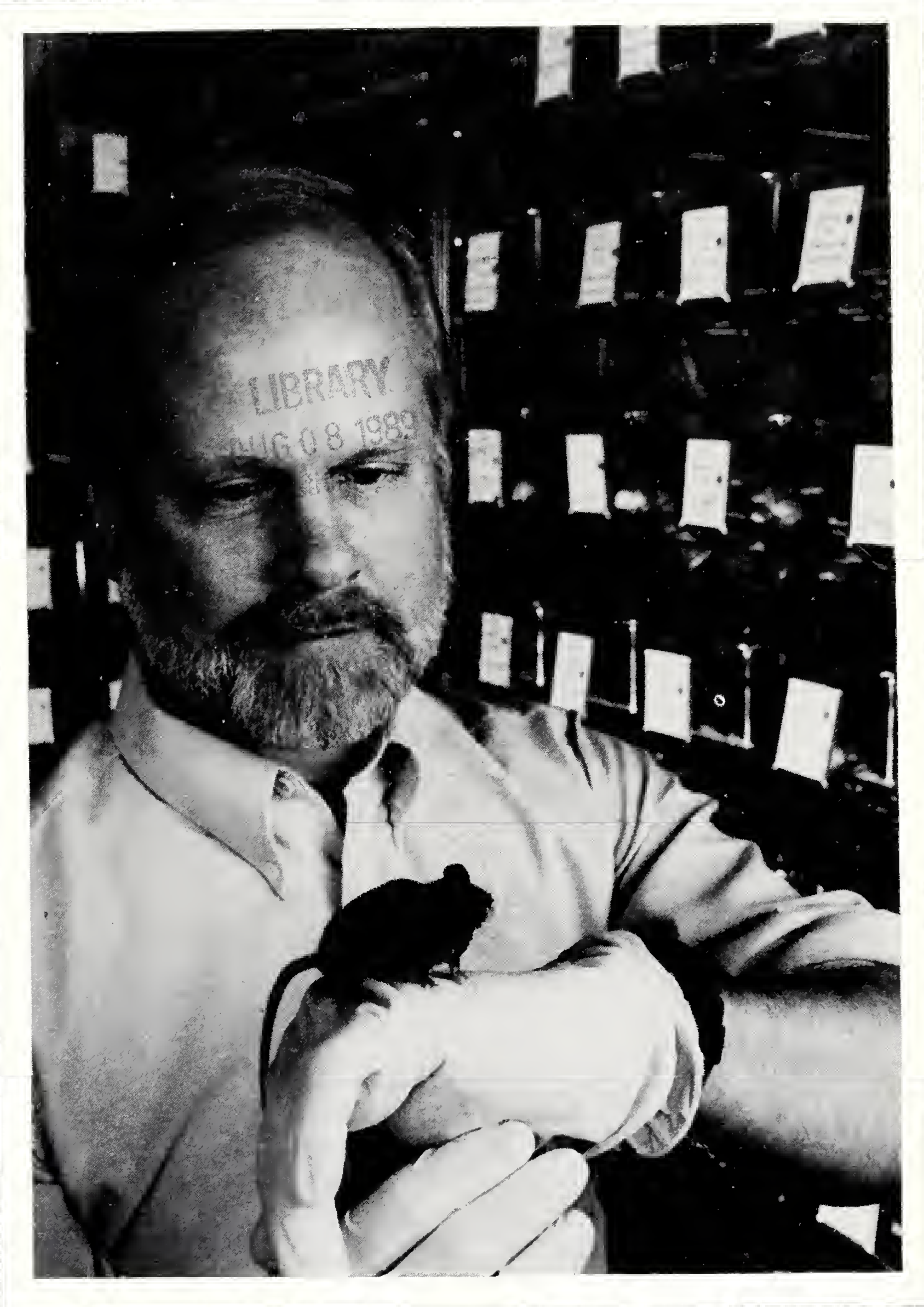
Simple Urine Test may Detect Early Bladder Cancer 12
American Diets Need Improvement 13



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See story on page 5

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from NIH

March 1989

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The Cover:

The mouse is being studied by NIAID investigators to better understand the effects that certain viruses have on the immune system and to screen for potentially promising AIDS drugs. The mouse model—called MAIDS for murine or mouse AIDS—shows similarities to human AIDS, including the development of lymphomas of the B lymphocytes, and the viruses that cause AIDS and MAIDS are closely related. See pg 5.

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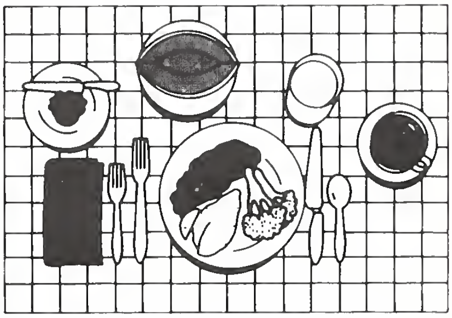
Cancer Nurses Play an Important Role in Research 16

NIH scientists have succeed in genetically modifying the pertussis or whooping cough toxin. Since current whooping cough vaccines can cause serious side effects, the genetically inactivated toxin, used as a vaccine, may prove to be safer. The modified toxin stimulates the immune response and cannot regain its disease-causing ability. See pg 2.

DNA probes are proving to be valuable tools in the early diagnosis of leukemia and lymphoma. The probes can accurately detect genetic alterations characteristic of cancer when the number of cancer cells is too small to be observed by other methods. With this advanced technology, treatment may be started earlier and its effectiveness evaluated. See pg 3.



According to a 24-hour dietary survey, Americans are not eating enough foods believed to be important in cancer prevention. These include fruits and vegetables rich in vitamins A and C, and high-fiber cereals and whole-grain breads. Consumption of these foods increased with increased income, and women were found to eat better than men, and people over 55 better than younger adults. See pg. 13.

Genetically Modified Toxin Could Be Basis for Improved Whooping Cough Vaccine

Laurie K. Doepel

Applying genetic engineering techniques, scientists have reported a major advance toward developing a safer pertussis, or whooping cough, vaccine. They have inactivated pertussis toxin, a pertussis bacterium product critical to the disease process, by modifying the toxin gene. This method of inactivating the toxin is virtually foolproof because the gene itself has been changed. While the mutant toxin is no longer harmful, it can still stimulate an immune response.

Used as the basis for a vaccine, this genetically modified toxin could potentially have fewer side effects than pertussis vaccines now licensed or in experimental use.

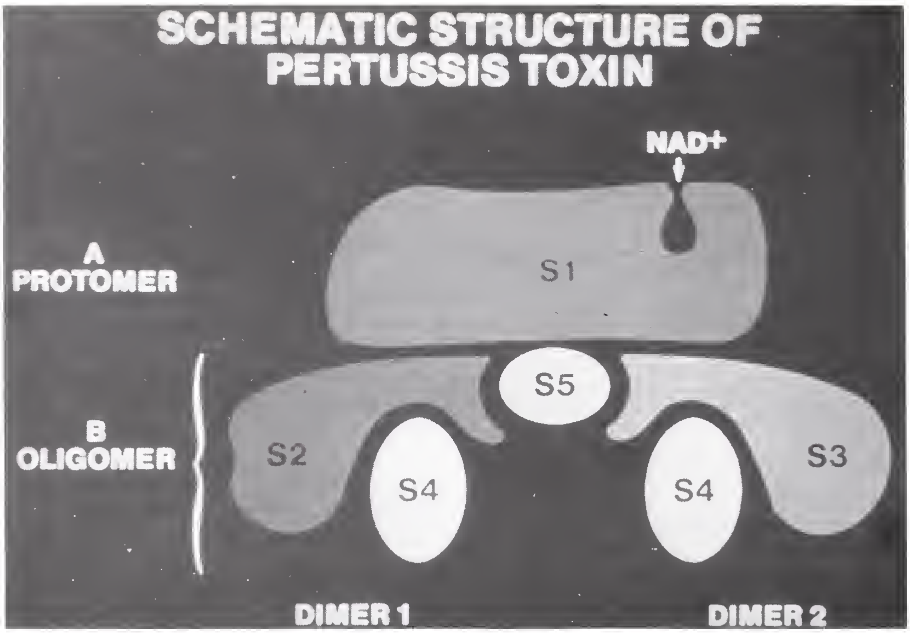
This research, reported in a recent issue of *Science*, was a collaborative effort by scientists at the National Institute of Allergy and Infectious Diseases (NIAID) Rocky Mountain Laboratories, Hamilton, MT; Amgen Inc., Thousand Oaks, CA; and the National Institute of Health, Tokyo.

Whooping cough is a particularly severe disease in the first year of life. It begins like a cold with an attendant dry cough but gradually evolves into spasms of uncontrollable coughing. In a small number of untreated children, the coughing can be so severe that the individual cannot get enough oxygen and consequently can suffer brain damage or even die.

Before introduction of the current whooping cough vaccine in the mid-1940's, U.S. deaths from whooping cough averaged between two and ten thousand per year; in 1986, there were six reported deaths due to whooping cough.

During whooping cough, the major toxin produced by the disease-causing organism, *Bordetella pertussis*, acts like a Jekyll and Hyde. On the one hand, the toxin stimulates infection-fighting proteins called antibodies—an essential characteristic for an effective vaccine. But it also initiates a series of biochemical events that essentially paralyzes the immune system of the infected host, permitting bacteria to grow in the lungs and as a result, cause disease.

In the present study, the investigators succeeded in uncoupling these incompatible effects by genetically turning off only that part of the toxin gene responsible for the disease-causing effects.



Color representation of the structure of the pertussis toxin. The A protomer (S1) represents the enzymatic portion of the toxin believed to have the primary responsibility for inducing the toxic effects of the molecule. The B oligomer portion includes five proteins, which are responsible for binding the toxin molecule to the cell and introducing the enzymatic A protomer to the inside of the cell. Photo courtesy of Jerry M. Keith, Rocky Mountain Laboratories, NIAID.

The project began 2-1/2 years ago after Dr. Jerry M. Keith's group at NIAID's Rocky Mountain Laboratories cloned the gene for the pertussis toxin and determined its genetic organization. They found that one part of the gene encodes for a single enzyme, dubbed S1, responsible for most if not all of the biological effects of the toxin.

These researchers, joined by their collaborators, then focused their efforts on S1 after determining that by deleting a small part of the genetic region coding for S1 they could eliminate enzyme activity. Using the tools of genetic engineering, they made precise mutations within this smaller genetic segment, thereby creating about 20 different mutant S1 molecules. Only one genetic mutation resulted in an S1 molecule that has virtually no enzymatic activity but that retains its ability to stimulate antibodies against pertussis. In this mutant S1, the genetic mutation caused only a single change in the building blocks, or amino acids, that make up the protein molecule.

Concern over the rare but serious side effects of the present whopping cough vaccine prompted the investigators to apply this novel approach toward vaccine development. The whooping cough vaccine now licensed in the United States is a whole-cell vaccine, so called because it contains the whole pertussis bacterium. The pertussis bacterium is grown and then killed, or inactivated, by heat treatment.

The whole-cell vaccine makes up part of the diphtheria-tetanus-pertussis (DTP) vaccine given in a series to very young children. The DTP vaccine has reduced the incidence of whooping cough in the United States from hundreds of thousands of cases per year to an average of one to three thousand cases per year. But some children—the American Academy of Pediatrics estimates 70 out of 19 million immunized each year—have severe reactions to the vaccine; in extremely rare cases, it can cause brain damage and even death. Exactly why this happens, however, is unknown.

Because newer acellular pertussis vaccines now in experimental trials contain only part of the pertussis bacterium, they also contain fewer biologic contaminants than do whole-cell vaccines, and therefore may be safer.

The acellular vaccines, however, are chemically inactivated. A chemically inactivated toxin may reactivate if it is not properly stored or mixed, and even after inactivation, tiny amounts of residual toxin activity can remain. Chemical inactivation is tricky: it depends on the chemical's ability to seek out and bind the toxin, and portions of the toxin molecule can infrequently be hidden and inaccessible.

In the current study the pertussis toxin was detoxified by changing its gene, and thus the inactive toxin cannot possibly regain its activity.

The challenge now is to recombine the mutant S1 molecule with the four other protein molecules that make up the toxin to determine whether this modified toxin, when incorporated into an acellular vaccine, provides protection against disease. ■

DNA Probes Useful in Early Detection of Certain Cancers

Jeffrey Cossman, M.D.

Recent developments in the use of DNA probe technology have provided a tool for the precise, sensitive detection of certain cancers. Now, even a single cancer cell can be detected in a patient. This approach has been used successfully in the early diagnosis of leukemia and lymphoma, which is the critical first step in the treatment of cancer.

Leukemias and lymphomas are cancerous growths usually originating from white blood cells, which play a major role in the body's immune defense system. Leukemias tend to populate the bone marrow and circulate in the blood, whereas lymphomas are solid masses in lymph tissues. There are more than 60,000 new cases per year in the United States affecting people of all ages, and these diseases are uniformly fatal if left untreated.

Fortunately, curative therapies are now possible for many patients. Treatment is more effective if given in early stages of the disease, before the malignant cells have had a chance to grow to overwhelming numbers. Moreover, the choice of therapy must be carefully tailored to each patient to destroy the particular type of leukemia or lymphoma afflicting that individual.

Precise diagnosis is necessary to determine the best course of treatment. The diagnostic analysis must: 1) accurately distinguish between leukemia/lymphoma and benign conditions that simulate them, and 2) classify the type of disease so that appropriate treatment can be selected.

The traditional tool of diagnosis has been the microscope under which cells obtained from the patient's blood or other tissues are examined for abnormal changes in appearance. While this technique has been used for more than a century, the recent revolution in molecular genetics has provided a new method for obtaining early and accurate diagnosis. The new approach is based on detecting specific genetic changes in malignant cells that distinguish them from normal cells. Now, research and hospital laboratories can use DNA probes to diagnose cancer more uniformly and do it with unprecedented sensitivity and accuracy.

The biological basis for diagnosing leukemia and lymphoma by molecular genetic techniques derives from a key characteristic of cancer cell growth, that is, a population of cancer cells is composed of genetically identical daughter cells (called a clone) spawned from a single precursor stem cell. In contrast, a collection of normal cells, such as normal white blood cells, is comprised of cells that are not genetically identical.

Genetic alterations are common in cancer cells and occur in many forms. Some are abnormal and are manifested as either a subtle abnormal change (such as a mutation) or as gross alterations affecting whole chromosomes, which may be broken, attached to other chromosomes, or duplicated. Both types of alterations can affect the molecular makeup of genes (DNA). For example, they may modify an oncogene—a specific type of gene that, for various reasons, can be turned on, leading to the transformation of the cell from its normal condition to a cancer cell that continually divides, grows, and spreads throughout the body. This process creates a population of cancer cells—derived from a single transformed precursor cell—each of which carries the same altered chromosome or gene.

Another type of genetic change that affects DNA is the normal rearrangement of genes carrying the code responsible for immunity. This occurs in lymphocytes, a specialized type of white blood cell, as they prepare to manufacture the wide variety of antibody proteins needed for the body's immune defense against bacteria, viruses, and other foreign invaders. Early in their development, lymphocytes shuffle their antibody genes as if they were a deck of cards. Like the many combinations of hands that can be dealt in a card game, shuffling of the genetic material generates a vast array of genetic combinations. The many new rearranged genes can, in turn, direct the production of tens of millions of different antibodies capable of recognizing and attacking virtually any of the potentially infectious agents to which we are exposed.

Many leukemias and lymphomas are derived from lymphocytes and carry rearranged antibody genes as would normal lymphocytes. Important here is that gene rearrangement in both normal and cancerous lymphocytes usually takes place early, *before* the cell repeatedly divides and grows. Thus daughter cells propagated from a single leukemia stem cell will all harbor the same gene rearrangement.

Any of the types of DNA alterations, whether due to chromosomal breakage, mutation or rearrangement, can serve as a diagnostic marker of cancer. These DNA markers can now be detected by laboratory tests using DNA probes. To diagnose leukemia or lymphoma, the DNA probe chosen may be an antibody gene or an oncogene corresponding to suspected areas of DNA alteration.

DNA extracted from a patient's blood, other fluids or samples from lymph node or bone marrow biopsies is cleaved into small fragments by enzymes that cut DNA at specific points. These fragments are then placed on gels to which electric current is applied that causes the fragments to move different amounts depending on their size. Each band is then transferred to filter paper. A radioactively labelled DNA probe is then applied to each filter paper. The probe seeks out its complementary strand of DNA in the sample and binds to it. The presence of the radioactive tag is determined, revealing the alterations by changes in the size of the DNA strand. The new DNA size provides a tumor marker since it is found uniformly in the leukemic, but not in normal, cells.

With this approach, a patient's blood or tissue sample may be found to be clonal, that is derived from a single cell, and, therefore, likely to be malignant. Furthermore, the type of leukemia or lymphoma can often be categorized by the specific oncogene that is rearranged.

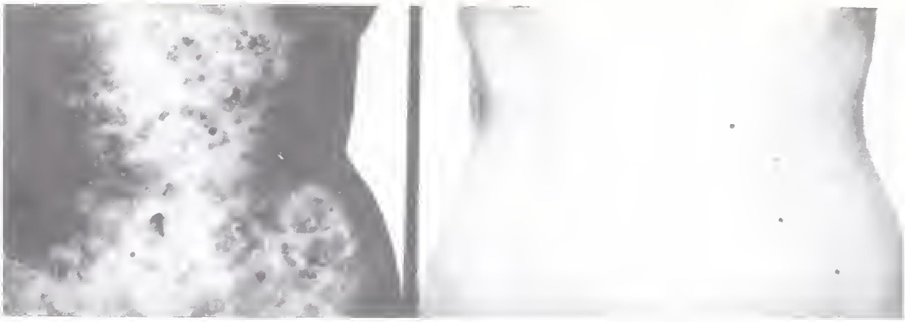
Through this use of DNA probes, remarkable progress has recently been achieved in the early detection of leukemia and lymphoma cells whose numbers are too few to be seen by any other method. In this case, a specific, altered DNA fragment found in the malignant cell, but not in normal cells, is copied millions of times to the point where it can be detected with a DNA probe. The technique, called the polymerase chain reaction (PCR), is so sensitive that even a single cancerous cell can be detected. This enhanced sensitivity will enable earlier diagnosis of leukemia and lymphoma and provide a new measuring stick to evaluate the effectiveness of treatment.

Diagnostic DNA probe analysis can be used for nearly all cases of leukemia and lymphoma and can be performed on any blood or tissue sample obtained from a patient. It is useful not only for making the initial diagnosis, but also for evaluating the spread of disease and for monitoring its course following therapy. Automation of DNA probe analysis for clinical hospital laboratories has progressed rapidly, paving the way for efficient transfer of this method from the research laboratory to the bedside.

With this advanced technology, the stage has been set for a new era in cancer diagnosis when all cancers may be diagnosed and appropriate therapy selected on the basis of DNA arrangement. ■

Treatment for Severe Psoriasis Gets Mixed Reviews: Some Reassurances, Some New Questions

Patricia Blessing



Before and after photos of a patient with severe psoriasis who received the PUVA treatment.

A 10-year study by researchers at 16 medical centers has shown that PUVA, an effective treatment for severe psoriasis, does not carry the major risks it was originally predicted to have. The greatest risk of PUVA—a combination drug and ultraviolet light therapy—was an increased chance of developing non-lethal, curable forms of skin cancer, according to two reports published in recent back-to-back issues of the *Journal of Investigative Dermatology.* The 1,380-patient study also found no increased risk of heart disease in patients with psoriasis, as earlier studies had suggested.

"For the most part, the news is reassuring," said Dr. Robert S. Stern at Beth Israel Hospital in Boston, Massachusetts, who headed the study and reported the results along with the other members of the Photochemotherapy Follow-up Study, which was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Because the study also showed an increased incidence of some tumors that may or may not be related to PUVA, Dr. Stern cautions that there is still some concern about the treatment's long-term effects.

Psoriasis—a chronic skin disorder characterized by red, scaly patches—affects as many as 3 to 4 million Americans, according to the National Psoriasis Foundation. Scientists do not yet know what causes psoriasis, but there are treatments that can temporarily clear the patches. Normally, skin cells mature, move up to the outer layer of skin in about 30 days, and are then shed. In psoriasis, this process is greatly hastened, occurring in about three days; the excessive immature skin cells "pile up" and form the elevated, scaly plaques on the skin's surface. When the disease affects major body areas, it can cause intense itching, dry, cracked skin, and swelling that can affect body movement and flexibility.

PUVA is one of the most common treatments of severe psoriasis (psoriasis that affects more than 30 percent of the body). PUVA combines the use of longwave light, ultraviolet light in the A range or UVA, with a photosensitizing drug called psoralen. When this prescription drug is taken internally, it sensitizes the skin to UVA light and slows down the reproduction of skin cells. An average person needs about 25 treatments to clear the psoriatic plaques. The effects can last from a few weeks to a year or longer.

Dr. Stern and his colleagues at the participating centers interviewed and performed annual physical exams on the psoriasis patients starting in 1976. The researchers documented each patient's use of PUVA throughout the 10 years, as well as other psoriasis treatments they may have received, such as UVB, topical tar, and ionizing radiation. They explored several diseases suspected of having a link to long-term PUVA therapy or to the disease itself: cardiovascular disease, two skin cancers (squamous cell carcinoma and melanoma), lymphomas, leukemia, and other cancers.

The study confirms earlier observations that PUVA patients are at higher risk for squamous cell skin cancer. The researchers also report that, although a greater incidence of basal cell skin cancer was observed in PUVA users, the increase was mild. Both of these skin cancers rarely spread beyond the skin tissue; with early detection, these cancers are easily removed.

In addition, the researchers found a strong relationship between the amount of PUVA exposure and risk of skin cancer. Patients who received more than 260 PUVA treatments were 12 times more likely to develop squamous skin cancer than were patients receiving fewer than 160 treatments.

Dr. Stern suggests that the increased risk of skin cancer could be reduced by alternating PUVA treatments with other psoriasis therapies. The amount of PUVA exposure also could be reduced by "going for 100 percent clearing of plaques initially, and waiting until substantial recurrence of the disease before treating again," he said.

The researchers found no association between heart disease and psoriasis—a link that had been suggested by earlier work.

As far as PUVA use and cancer incidence and mortality, the researchers found that overall the rates in the study population were comparable to those in the general population. The cancers the researchers were most concerned about were melanomas, lymphomas, and leukemias, and they found no increased risk for these cancers in the PUVA-treated population.

Yet, when the researchers examined their data for other cancers, mainly breast and colon cancers and brain tumors, some questions and concerns were raised. Small (2- to 3-fold) increases in breast cancer and colon cancer were found in the PUVA patients. Dr. Stern believes, however, that because the study design did not include known risk factors for these cancers, such as family or childbearing history, a degree of risk is unlikely to be associated with PUVA.

He is concerned, however, about the finding that patients in the study group were five times more likely than expected to develop brain tumors. The question remains, Dr. Stern said, whether this increase is due to PUVA therapy or perhaps to petroleum products in topical tar applications used by many psoriasis sufferers, including patients in this study, to control their psoriasis.

Dr. Stern speculates that exposure levels and predisposed susceptibility to petroleum products might put some persons at greater risk. "It's something that will have to be watched," he said.

"Overall, we found that the most worrisome aspects thought to be associated with PUVA do not appear to be major problems after a decade of study," Dr. Stern concluded. "PUVA is quite an effective therapy that should be used judiciously, not as an absolute therapy for severe psoriasis, but in conjunction with other therapies, so that the major risks can be reduced." ■

AIDS in the NEWS

Mouse Model of AIDS Useful in Identifying AIDS Drugs

Sandy Hecker

A new mouse model for AIDS may help researchers further define the pathogenesis, or disease-causing effects caused by certain viruses that infect the immune system. The virally infected mice are also expected to hasten the identification and development of drugs effective against HIV.

The mouse model has many parallels with clinical manifestations of ARC (AIDS-related complex) and AIDS, says Dr. Herbert C. Morse III, Chief, Laboratory of Immunopathology, National Institute of Allergy and Infectious Diseases (NIAID). When infected with murine leukemia virus (MuLV), the mice develop swollen lymph nodes and spleens, high levels of antibodies (potentially protective proteins produced by the immune system), profoundly depressed immunity and increased susceptibility to infections. These symptoms of viral infection are similar to those seen in persons infected with HIV. An especially important parallel with human AIDS is that the mice develop lymphomas of their antibody-producing cells (B lymphocytes).

Dr. Herbert C. Morse, Chief, Laboratory of Immunopathology, NIAID, uses the mouse model in AIDS research.

The mouse model—called MAIDS, for mouse or murine AIDS—may be useful for the development of drugs to kill the viruses that cause AIDS and MAIDS, called retroviruses. These viruses contain ribonucleic acid (RNA) rather than the closely-related, deoxyribonucleic acid (DNA) by which most organisms—including humans—store their genetic information. Therefore, to use the genetic machinery of human or animal cells to replicate, the viruses must convert their genetic material to DNA. Retroviruses contain an enzyme—called reverse transcriptase—to do this.

The viruses that cause AIDS and MAIDS both use reverse transcriptase and are closely related; consequently, this mouse model is useful for screening drugs that may kill HIV in humans. This mouse model is presently being used for preliminary AIDS drug screening in several laboratories around the United States.

Collaborators include Drs. S. Peter Klinken, Torgny N. Fredrickson, Janet W. Hartley, and Robert A. Yetter, NIAID. This research is also supported by the Leukemia Society of America. ■

AIDS Regent Repository Catalog Now Available

Sandy Hecker

The NIH AIDS Research and Reference Reagent Program Repository Catalog is now available from the National Institute of Allergy and Infectious Diseases (NIAID). The catalog, which will be updated biannually, lists all reagents currently available from the repository. The repository is fully operational and continuing to acquire additional reagents from AIDS researchers throughout the world.

Research on the human immunodeficiency virus (HIV, the cause of AIDS) and its interactions with cells it infects, often requires difficult-to-obtain experimental materials. The repository was established in April to expedite availability of such materials. Total projected funding for the repository is approximately $7.7 million for 1988 through 1992. Approximately 1400 AIDS researchers worldwide (chosen from the scientific literature) were surveyed to determine which reagents are most critically needed in a repository. Results of this survey have guided and continue to guide repository acquisitions.

The reagents are available to qualified investigators worldwide—both established and newly recruited—whose research relates to AIDS. Currently available materials include clones of HIV-1, HIV-2 (the AIDS virus found primarily in West Africa), the closely related simian immunodeficiency virus (SIV), other related retroviruses, uninfected cell lines that support the growth of these viruses, cells chronically infected with retroviruses, and plasmids that express viral proteins. The repository also contains reference antisera (antibodies), and monoclonal antibodies to specific viral antigens. Biological response modifiers such as lymphokines, cytokines, and monokines (cellular hormones that influence cell function), and chemicals or drugs used to modulate the immune system will be made available to the scientific community.

The repository will develop and distribute standardized protocols for viral isolation, as well as titration and neutralization assays. Standardized biochemical assays for evaluating compounds with antiviral potential will also be made available at a future date.

All reagents are available in quantities sufficient to compare with the activity or purity of proteins being obtained by research laboratories. Comparison of various reagent samples by the repository scientists will allow standardization of reagents within the repository and determination of the most active products, as well as quality control of the collection.

To foster the free exchange of reagents, materials from the repository are provided for research purposes only. Before obtaining a reagent, the recipient must agree that he or she will not transfer the material to a third party. Donors of a reagent routinely obtain information about each request for the reagent, acknowledgement as the source of the reagent in the repository's biannual catalog of reagents, and acknowledgement as the source of the reagent in published work associated with its use. Reagents are not available for therapeutic use or for commercial purposes.

NIAID itself needs access to sources of AIDS research-related reagents to support its rapidly expanding AIDS research efforts. Researchers working at NIH, as well as at NIAID-supported National Cooperative Drug Discovery Groups, National Cooperative Vaccine Development Groups, AIDS Clinical Trials Units, Programs of Excellence for Basic Research on AIDS, Centers for AIDS Research, and International Centers for AIDS Research all require a myriad of reagents. Although some of the reagents needed for AIDS research are available from NIH and other laboratories, a centralized resource is able to acquire, store, and standardize a greater number of reagents more efficiently than individual laboratories.

The repository will be represented at all appropriate scientific meetings. The NIH repository is designated one of the World Health Organization repositories and is collaborating with WHO and its repositories in Paris, France, and in London, England, to make the repository available to AIDS researchers worldwide.

To obtain a catalog of reagents available from the repository and sample forms for donating or requesting reagents, write to

Repository Catalog
c/o ERCI Facilities Service Corporation
649A Loftstrand Lane
Rockville, MD 20850■

New NIAID Program Expands Study of Drugs in Children with Aids

Elaine Baldwin

The National Institute of Allergy and Infectious Diseases (NIAID) has established a new program that will greatly expand clinical trials of experimental drugs in children with AIDS. The Institute has awarded $8.8 million to 11 medical centers that will join NIAID's nationwide network of 34 AIDS Clinical Trials Units now conducting AIDS treatment research.

Since 1981, more than 1100 children in the United States have been diagnosed with AIDS, and two or three times that many are believed to be infected with the human immunodeficiency virus (HIV), the cause of AIDS. Nearly all pediatric AIDS cases are caused by transmission of HIV from pregnant women to their unborn children.

In commenting on the awards, NIAID Director Anthony S. Fauci, M.D., said, "AIDS is an increasingly grave threat to children in the United States and in many other countries. The impact of pediatric AIDS on families is devastating, and the growing numbers of children infected with HIV are straining medical and social services in some cities. Through the establishment of these Pediatric AIDS Clinical Trials Units, we hope to speed progress in finding effective methods of treating HIV infection in children."

The AIDS Clinical Trials Units and their affiliated institutions, together with NIAID's AIDS Program and a center for data management and analysis, make up a consortium called the AIDS Clinical Trials Group (ACTG). ACTG members collaborate in the evaluation of innovative and high priority therapies for HIV infection and AIDS-related opportunistic infections and cancers. Two previously funded units, at Children's Hospital, Boston, and the University of Medicine and Dentistry of New Jersey, Newark, are designated pediatrics units.

"By establishing units specifically devoted to pediatric AIDS research," Dr. Fauci said, "we can address the unique needs of this population." He said that pediatric AIDS differs from HIV-related disease in adults in several respects, and treatment approaches must be tailored to those special characteristics.

Like adults, children with AIDS develop life-threatening opportunistic infections. Such infections are caused by other viruses, bacteria, parasites, or fungi that are usually fought off successfully by people whose immune systems are functioning properly. Children rarely have the AIDS-related cancers seen in adults with HIV infection. However, HIV-infected children typically develop severe, frequently recurring bacterial infections because their immune systems are unable to manufacture specific antibodies.

During the past two years, ACTG investigators have been conducting several clinical trials of experimental therapies in HIV-infected children with symptoms of AIDS. They are evaluating the effectiveness of the antiviral drug AZT in countering HIV activity and intravenous gamma globulin in reducing bacterial infection. The pediatric units will conduct studies of promising new experimental therapies as they become available.

In preparation for possible early intervention studies, the units are expected to develop ways of identifying HIV infection in fetuses and infants. Commonly available tests do not distinguish between antibodies the child generates against HIV infection and antibodies transmitted from the mother that will eventually disappear. Recently, scientists have reported on a new technique, still in the research stage, that can aid in distinguishing between true and apparent infection in babies born to infected mothers.■

Rising HIV Infection in Zairian Hospital Workers Due to Heterosexual Spread

Elaine Baldwin

A high and increasing prevalence of HIV infection among hospital workers in Kinshasa, Zaire, indicates how the virus is spreading in the general community. HIV infection in Kinshasa hospital employees is apparently unrelated to occupational exposure.

NIAID scientist Dr. Thomas C. Quinn and his colleagues at Project SIDA in Kinshasa reported this finding in a recent issue of the *New England Journal of Medicine*. At the Stockholm AIDS meeting in June, Project SIDA investigators reported that more than 80 percent of new cases of HIV infection in Kinshasa are due to heterosexual activity.

"The Project SIDA studies give us an indication of how HIV progresses in a population of non-drug-abusing heterosexuals," Dr. Quinn said. "We in the United States must realize that no group can be complacent about the risks of HIV transmission. Changes in sexual practices are essential to prevent the spread of HIV."

Although AIDS is widely recognized as a burgeoning and potentially catastrophic health problem in some parts of Africa, little information exists on the rate of increase of HIV infection in various African countries. Present knowledge of the natural history of HIV infection is based almost entirely on studies of homosexual and bisexual males and intravenous drug abusers in developed countries.

Beginning in 1984, the investigators initiated a prospective study tracing the natural history of HIV infection in a cohort of more than 2000 employees at Kinshasa's Mama Yemo Hospital, including physicians, nurses, and laboratory, clerical and manual workers. They found that HIV prevalence in this group as a whole rose from 6.4 percent to 8.7 percent between 1984 and 1986. Similar rates occurred in pregnant women attending an antenatal clinic and blood donors surveys at other Kinshasa hospitals.

Based on these results, the Project SIDA investigators estimated that 32,000 persons in Kinshasa probably became newly infected with HIV during the two-year span. The total population of Kinshasa is approximately 3 million.

AIDS in the NEWS

The 1984 Project SIDA study showed a correlation between HIV seropositivity and being young and unmarried or having had a blood transfusion. The followup study showed that prevalence rates did not vary according to type of employment at the hospital. HIV seropositivity was about the same for clerical workers with little patient contact and for physicians and lab workers with frequent exposure to AIDS patients and their body fluids. A relatively higher rate of infection among nurses, the authors concluded, was due not to hospital exposure but to being young, female and unmarried. ■

NIAID Joins with Biotech Company to Test Promising Recombinant AIDS Drug

Elaine Baldwin

The National Institute of Allergy and Infectious Diseases (NIAID) and Biogen, Inc., a biotechnology company located in Cambridge, Mass., are sponsoring clinical tests of a genetically engineered drug that promises to block the AIDS virus in humans.

Researchers at Massachusetts General Hospital and Cedars-Sinai Medical Center, Los Angeles, will study Biogen's version of recombinant soluble CD4 in patients infected with the AIDS virus. The two medical centers are part of NIAID's AIDS Clinical Trials Group, a nationwide, multicenter network of experienced clinical investigators who collaborate in the evaluation of experimental drugs for AIDS and AIDS-related conditions.

The Phase I dose escalation study, which is designed to determine the safety of the drug in humans, will be conducted initially in approximately 25 patients with AIDS and AIDS-related-complex.

The human immunodeficiency virus (HIV), which causes AIDS, cripples the immune system by attacking and destroying specific immune cells, especially T4 cells and monocyte/macrophages. These and a few other cell types have on their surfaces a receptor, a protein known as CD4. Scientists have shown that to gain entry into human cells, the envelope (outer coat) protein of HIV attaches to the CD4 receptor. This discovery spawned the idea of cloning copies of the CD4 molecule or parts of it, and then trying to fool the AIDS virus into attaching itself to this free-floating or soluble CD4 rather than to healthy cells.

Through genetic engineering, scientists in a number of laboratories have made synthetic versions of CD4. Their products are called recombinant soluble CD4, or rCD4, or recombinant soluble T4 receptor analogue. In the test tube, these products have been shown to bind to HIV and neutralize the activity of the virus. These findings have generated great interest among researchers attempting to find new drugs to treat persons infected with HIV.

Scientists at Biogen, in collaboration with researchers at Massachusetts General Hospital, showed in laboratory experiments that their recombinant soluble CD4 product blocked direct infection of T4 cells by HIV as well as cell-to-cell transmission of the virus.

Biogen scientists head one of NIAID's 18 National Cooperative Drug Discovery Groups (NCDDGs), which are teams of experts from biotechnology companies, pharmaceutical houses, universities, medical centers, and federal agencies. The overall goal of the NCDDGs is to develop new AIDS drugs targeted to specific cellular or viral proteins. Smith, Kline and French and GeneLabs, both participants in the NCDDG program, also have CD4 products in preclinical research.

During the past year, the staff of the NIAID AIDS Program has been working with these groups and others to bring CD4 products to clinical trials. The Institute is collaborating with Genentech, which recently launched the first human trials of rCD4 at three medical centers. If the data from these studies are promising, NIAID will encourage the various companies to conduct further studies through the NIAID AIDS Clinical Trials Group.

The NIAID/Biogen study will be conducted by Robert Schooley, M.D., Massachusetts General Hospital, Boston, a Harvard Medical School affiliate, and David Ho, M.D., Cedars-Sinai Medical Center, University of California, Los Angeles. ■

Genetic Defects Found in Severe Forms of Diabetes

Charlotte Armstrong

Scientists at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) reported in *Science* on their identification of two specific mutations underlying a case of leprechaunism, a rare inherited disease marked by severe diabetes. The work demonstrates how such mutations can disrupt the molecular basis of glucose metabolism, which is abnormal in diabetes, and illustrates how more common forms of diabetes possibly might be traced to similar inherited defects.

The mutations found in these patients are located in the gene that controls the structure of the cellular receptor to insulin, a hormone that controls glucose metabolism. Insulin must bind to the receptor to act. In the same issue of *Science*, scientists at the University of Chicago and the University of Kyoto, Japan, report identifying a distinctly different mutation in the human insulin receptor gene in two patients with a different inherited syndrome marked by severe diabetes. The work of the Chicago group was funded in part by NIDDK. These reports are the first to specify precisely genetic mutations that cause diabetes by affecting the insulin receptor.

Diabetes impairs the body's ability to use its primary source of fuel—glucose, a form of sugar—for energy. In the most common form of diabetes, noninsulin-dependent diabetes mellitus or NIDDM, the body responds inadequately to insulin, a condition called insulin resistance. While an estimated 11 million Americans have some form of diabetes, the cause or causes of this disease remain a mystery.

Drs. Simeon Taylor and Takashi Kadowaki and colleagues at NIDDK analyzed a segment of the genetic material, or DNA, that dictates the structure of the insulin receptor in their patient with leprechaunism. (Leprechaunism is a syndrome that is associated with a number of physical defects, in addition to extreme insulin resistance.) They determined the sequence of DNA bases—the links in the molecular chain that make up DNA—in the receptor gene and compared it with the sequences of normal receptors that have been identified in earlier research.

In two locations the receptor DNA from the patient with leprechaunism was different from the normal receptor gene by one DNA base. One of the base substitutions results in abnormal binding of insulin to the receptor. The other substitution results in a receptor molecule that is stunted. The investigators demonstrated that this abnormal receptor never takes its position on the cell surface to bind with insulin.

The NIDDK group was then able to trace each mutation back to the parents. The patient's mother has the mutation that causes abnormal binding of insulin to the insulin receptor and passed this on to her child. The father carried, and transmitted, the mutation that causes the incomplete receptor. Each mutation alone is relatively benign. The mother has normal glucose metabolism, while the father has mild insulin resistance, a condition that often precedes diabetes. (It is common for NIDDM to become manifest after middle age, so he may still develop diabetes later in life.) However, the result of inheriting these two different mutations is a potentially lethal degree of insulin resistance in the child.

In their patient, the Chicago researchers identified a distinctly different defect in the insulin receptor gene. Drs. Donald Steiner and Yasunao Yoshimasa and colleagues at the University of Chicago collaborated with Dr. Takako Kakehi and colleagues at the University of Kyoto in studying two sisters with type A insulin resistance. This disorder, like leprechaunism, is characterized by extreme insulin resistance and a number of other physical defects.

The scientists found that each woman had inherited two copies of one mutation that altered the insulin receptor structure in such a way that the precursor molecule for the receptor was not cleaved, or cut, in the manner that normally results in the fully functioning receptor. The parents of these patients were blood-related, increasing the chances that they had mutations in common. Thus, their daughters received one copy of the mutations from each parent. While the parents were not available for blood testing, the mutation they carry in a single dose appears benign.

In most cases, the cause of NIDDM is unknown. Scientists believe that NIDDM has no single cause but results from different cellular defects, many of which can impair the function of insulin and lead to the symptoms of diabetes. Studying NIDDM is difficult, however, because the effects of the disease can be subtle and variable. Studying rare diseases like leprechaunism and type A insulin resistance provides insights into the more common illness.

In addition, the new techniques and information from basic genetic research such as the ability to sequence the receptor genes of parents and child, along with information about the normal receptor sequences from previous research, made possible these studies of insulin resistance.

The identification of glucose intolerance in the father of the patient with leprechaunism illustrates that such mutations, in the carrier state, may contribute to some proportion of NIDDM. If the father develops NIDDM, he will join millions in this country who have the disease. Scientists estimate that half of those with NIDDM don't know they have it. NIDDM is a risk factor for serious long-term complications that affect the heart, eyes, nerves, and kidneys, making diabetes a leading cause of death and disability in the United States.

Even if the mutations underlying these very rare syndromes are too uncommon to play a role in most cases of NIDDM, this work illustrates how a genetic misstep in the molecular instructions for glucose metabolism can result in the illness we know as diabetes. A precise definition of the molecular basis for diabetes provides new avenues for prevention or treatment, including gene therapy. ■

Old Drug Gets New Use in Preventing Parasitic Infection Among Travelers

Leslie Fink

Results from a new study show that a drug long used to ward off heartworms in the family dog also prevents a parasitic disease that occurs among human visitors to regions of Africa, where the worm is common. By killing the parasite, known as *Loa loa* or African eyeworm, before it becomes established in the body, the drug prevents the powerful immune reaction that makes the infection severely debilitating.

According to Drs. Thomas Nutman and Eric Ottesen, parasitic disease experts at the National Institute of Allergy and Infectious Diseases, none of the 41 Peace Corps volunteers who received the drug, diethylcarbamazine, became infected with the *Loa loa* worm. Six of the 60 volunteers who took a placebo, however, developed the infection, known as loiasis.

Dr. Nutman and his colleagues reported their findings in a recent issue of the *New England Journal of Medicine*.

While an estimated 13 million people living in Western and Central Africa are infected with the worm, the disease appears to be most serious among newcomers to these regions. In these people, the immune system is especially sensitive to the invading worms. Such travelers would include Peace Corps workers, missionaries, State Department employees, anthropologists, and journalists on assignment abroad.

"For those whose risk of exposure to the parasite is high or prolonged, weekly

A blood sample viewed under the microscope contains a very early larval stage, or microfilaria, of the *Loa loa* worm (magnified 40X). The dark staining spots nearby are white blood cells.

The adult form of the *Loa loa* worm is also called the African eye worm because it often crawls under membranes covering the eye.

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diethylcarbamazine should be used to prevent *Loa loa*," the report says. In addition, the authors say, the weekly, 300-milligram dose used in the two-year study "is quite safe."

Because exposure to the parasite must be intense or for long periods before infection can develop, the scientists do not recommend the treatment to short-term visitors to major cities in these regions. "This is not for casual visitors who stay in hotels in the big cities," says Dr. Ottesen.

Loa loa is a microscopic worm transmitted from person to person by certain flies that feed on human blood. During a bite, the fly infects a person with an immature form of the worm. Adult worms, which take up residence under the skin, are called eyeworms because they also frequently crawl under the membranes of the eye.

Travelers who visit regions where *Loa loa* is found respond severely to the parasite because their immune systems are inexperienced in dealing with the worm. In these people, the immune system sets up an unusually strong reaction to the parasite, which results in organ damage that is sometimes "major and life-threatening," the authors say.

According to the report, diethylcarbamazine kills the immature worms before the immune system launches its attack. This in turn prevents damage to the heart and kidneys, the most serious aspects of the infection among newcomers to regions where the worm is common.

Dr. Nutman and his coworkers studied a group of Peace Corps volunteers working in Gabon, Cameroon, or the Central African Republic. Sixty of the subjects took a placebo once a week, while 41 took diethylcarbamazine. Neither the scientists nor the volunteers knew which subjects took which pill.

After two years, when the codes were broken, the researchers found that none of the subjects taking diethylcarbamazine developed loiasis, while six of those taking the placebo did. All six of the infected subjects had been working in Gabon, where prevalence of the worm is much higher than in the other countries. In the Gabon group, 14 of the placebo takers and all of those who took diethylcarbamazine were free of infection.

While some subjects reported mild nausea, diethylcarbamazine was "not associated with significant adverse reactions," even though some workers took the drug for two years.

The authors conclude that "diethylcarbamazine given orally once a week can be an effective, acceptable [drug] to prevent loiasis in temporary residents of regions of Africa where *Loa loa* is endemic." ■

NATIONAL INSTITUTES OF HEALTH

Exhibit on Older Americans Tours the Nation

Barbara Katzman

Each of the 172 embroidered blocks of this quilt represents a significant moment in the artist's life on the farm.

An unusual exhibit of art and stories by older Americans, designed to foster communication between generations, is traveling around the United States. Developed by the Office of Folklife Programs of the Smithsonian Institution and supported by the National Institute on Aging (NIA) and others, "The Grand Generation: Memory, Mastery, Legacy" is on a 2-1/2 year, 15 museum tour.

The exhibit consists of some 60 objects combined with photographs and text about the contributors—people over the age of 65—who have enriched American folklore. For example, in one area of the exhibit, hangs an embroidery depicting the three stages of Ethel Mohammed's life—childhood, parenthood, and old age. Ms. Mohammed accomplished the stitchery at age 77 as a form of life review.

Several of the entries portray artforms not readily identified by young museum visitors—coopering, whittling, barrel making, and woodcarving. The exhibit highlights the almost lost art of Appalachian cooper Alex Stewart, 84, who constructs and repairs wooden casks or tubs. Grandson Rick and his contemporaries learn what can be constructed from wood without so much as a nail or a bottle of glue. At age 90 Jehu Camper believes his whittling will assist youngsters to better understand their own personal histories. Toward this end, he has contributed a wooden farmyard scene complete with haystacks and other reminders of past years. A miniature saddle made by 68-year-old master saddler Duff Severe of Pendleton, Oregon is on display, as is a treasure chest of heirlooms amassed by Helen Fretz Jarrett, 83, of Washington, D.C. as a gift for her grandson on his 11th birthday. Designed to preserve and enliven the past, the exhibit also includes such items as quilts, needlework, woodcarvings, paintings, marionettes, photographs, ceramics, and even baked goods made from dog-eared recipes. Many youngsters who visit the exhibit express respect and admiration for these forgotten crafts and for the people who have contributed to the exhibit.

The project serves to give young people a rare opportunity to learn first-hand of the rich heritage passed down from generation to generation. According to folklorist Marjorie Hunt, Curator for the Office of Folklife Programs at the Smithsonian Institution and project director, "The vital cultural role of the elderly made visible through their knowledge, skills and artistry provides us with a sense of continuity and an essential link to the past." Several sites have successfully expanded the exhibit to include local, older artisans.

To further encourage dialogue between generations the exhibit offers a booklet entitled, "The Grand Celebration" which instructs readers of all ages in the art of conducting interviews and obtaining verbal histories. Through stories, artforms, memories, and keepsakes the treasury of knowledge from the past will enrich present day experiences and enhance future years. (The pamphlet is available by sending $1.50 to SITES, Smithsonian Institution, Washington, D.C. 20560.)

The concept for this exhibit grew out of the 1981 White House Conference on Aging when the Smithsonian Institution, supported by the NIA, launched a program entitled, "Tools for the Harvest." The initial purpose was to interweave cultural and humanistic components into the conference. The successful completion of that project fueled the Festival of Folklife 1984 at the Mall in Washington, D.C. "The Grand Generation: Folklife and Aging" met with such enthusiasm that a follow-up activity was initiated. With support from the NIA, the Administration on Aging, the May Department Stores Company, the American Association of Retired Persons, and the Women's Committee of the Smithsonian Associates, the plans became reality.

Also featured in the exhibit is this churn crafted by Appalachian cooper Alex Stewart and the bucket made by his grandson Rick Stewart. Both are from Hancock County, Tennessee.

Ethel Mohammed is one of the contributors—people over the age of 65—to "The Grand Generation: Memory, Mastery, Legacy."

The Grand Generation exhibit is traveling under the auspices of the Smithsonian Institution. The remaining itinerary for "The Grand Generation: Memory, Mastery, and Legacy" is:

1988	
September 3– October 2	Gibson Art Gallery State University College Potsdam, New York
October 22– November 20	Arizona State University Phoenix, Arizona
December 10– January 8	Bishop Museum Honolulu, Hawaii
1989	
January 28– February 26	Butler Institute of American Art Youngstown, Ohio
March 18– April 16	Children's Museum Indianapolis, Indiana
May 6– June 4	Michigan State Univ. Museum East Lansing, Michigan
June 24– July 23	Pioneers Museum Colorado Springs, Colorado
August 12– September 10	Fullerton Museum Fullerton, California
September 30– October 29	Robinson State Museum Pierre, South Dakota
November 18– December 17	Robinson State Museum Pierre, South Dakota
1990	
January 6– February 4	Iowa Historical Society Museum Des Moines, Iowa

A full-color exhibit catalogue produced by Ms. Hunt and colleagues Mary Hufford and Steven Zeitlin reinforces the uniqueness of the project. The catalogue can be obtained by writing to: University of Washington Press, P.O. Box 50096, Seattle, Washington 98145 ($25. for hardbound and $14.95 for soft cover). ■

This miniature saddle, made by 68-year old master saddlemaker Duff Severe from Pendleton, Oregon, is also on display.

Helen Jarrett, age 83, of Washington D.C. assembled this treasure chest of family heirlooms as a special gift for her grandson Billy on his eleventh birthday.

Urine Test May Aid in Early Detection of Bladder Cancer

Elaine Blume

Scientists at the National Cancer Institute (NCI) have developed a relatively simple urine test that shows promise of detecting bladder cancer at an early, potentially curable stage. Currently, diagnosis and follow-up of this common cancer entails invasive and often painful procedures, and some cases are not discovered until after the disease has spread and can no longer be cured.

The new test could make it feasible to test patients when there was even a slight suspicion of bladder cancer and could make it much easier to monitor bladder cancer patients for recurrences following treatment.

The test, described in a recent issue of the *Journal of the National Cancer Institute*, works by detecting a protein known as autocrine motility factor (AMF) in the urine samples of patients. AMF is secreted by cancer cells and induces movement of these cells. The substance plays a key role in enabling cancers to spread locally and to metastasize to distant sites.

Raouf Guirguis, M.D., Ph.D., Elliott Schiffmann, Ph.D., and their co-workers in NCI's Laboratory of Pathology measured levels of AMF in 24-hour urine samples from 22 patients with bladder cancer and 27 patients with non-cancerous conditions of the urinary tract. The study was conducted on a "blind" basis; that is, the researchers were not informed of the clinical and pathologic diagnoses until after they had evaluated the urine samples.

The researchers developed and used two methods to measure AMF in the samples. The first method tested the effect of the urine on the motility of selected "responder" cells. Urine samples with high levels of AMF induced a higher proportion of responder cells to pass through artificial membranes than samples containing little or no AMF. The second method, an immunologic test of a type known as ELISA, was used to confirm the motility assay results.

Dr. Guirguis and his co-workers found that the urine samples fell into two distinct groups. One group of samples had high levels of AMF, while the other group had low levels or none. When these results were compared with the clinical diagnoses, the researchers found that the group of urine samples with high AMF levels had come from patients with bladder cancer, while the remaining samples were from patients with benign (non-cancerous) conditions.

In the 49 tests, there were two false positives, one marginal false positive, and no false negatives. In some instances where clinical diagnoses and AMF test results disagreed at first, subsequent more definitive diagnoses confirmed the AMF assay results.

Levels of AMF were highest in urine samples from patients whose cancers were most invasive (i.e., had the greatest tendency to spread). The assay also proved highly accurate in detecting recurrence of bladder cancer following treatment.

"AMF appears to show specificity for the tumor and is only expressed in very low amounts under normal or inflammatory conditions," notes Dr. Guirguis. "Cell migration is not common in normal epithelial cells. So when we find AMF, it is likely to signal the presence of an invasive tumor."

The scientists estimate that it will be at least two years before a urine test for AMF moves into clinical trials. During that time, AMF must be measured in many more samples. "So far," says Dr. Schiffmann, "we have looked at only a limited number of samples, though they represented a variety of different physiological conditions." The trials would be designed to confirm that the urine test was useful in diagnosing bladder cancer and detecting recurrences.

Meanwhile, a number of clinicians are following this work with great interest. In an editorial accompanying the article, F.K. Mostofi, M.D., of the Armed Forces Institute of Pathology, noted that "the specificity and the simplicity of the procedure and the fact that it can be done on voided urine would make this one of the most valuable tests in the care of patients with cancer of the bladder." Currently, bladder cancer patients must undergo numerous invasive tests in order to monitor their condition.

Ultimately, the scientists hope to modify their assay so that it can be used to measure AMF in blood, making it possible to detect cancers from all parts of the body.

More than 46,000 people develop bladder cancer each year in the United States, and many of these cases recur despite treatment. The disease is responsible for about 10,000 deaths annually. The five-year relative survival rate has been 77 percent for patients diagnosed with bladder cancer between 1979 and 1984, the most recent years for which population-based survival data are available. ■

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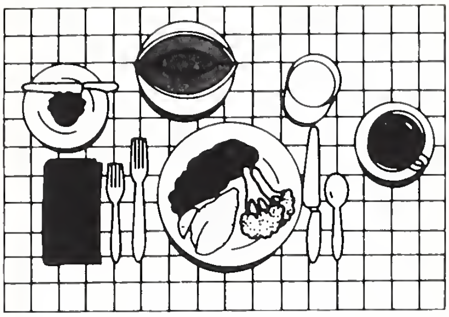


American Diets Found to be Far From Ideal

Cori Vanchieri

"Americans are just not eating enough fruits and vegetables and whole-grain cereals, even though these are potentially the most beneficial foods for preventing cancer," said Blossom Patterson, M.A., lead investigator of a new National Cancer Institute (NCI) study of eating patterns in the United States.

On the day of the survey, more than 40 percent of the U.S. adult population did not eat even a single fruit and approximately 20 percent did not eat a vegetable. Also ignored were high-fiber cereals and whole-grain breads which, along with fruits and vegetables, are good sources of fiber. More than 80 percent of those surveyed did not consume any high-fiber cereals or whole-grain breads on the day of the interview.

Published in a recent issue of the *American Journal of Public Health*, the study provides detailed estimates of the proportions of U.S. blacks and whites who eat foods thought to contribute to or to protect against cancer development. The researchers looked at 24-hour dietary recall data collected between 1976 and 1980 during the second National Health and Nutrition Examination Survey (NHANES II) conducted by the National Center for Health Statistics.

Patterson said that the data should still largely reflect current eating patterns, particularly for fruits and vegetables, based on U.S. Department of Agriculture (USDA) Continuing Survey data that showed only minimal changes in the consumption of these foods between 1977 and 1986.

"In terms of eating a cancer prevention diet, women in our study ate better than men and people over 55 had better diets than younger adults," said NCI's Gladys Block, Ph.D., coauthor of the study. "Even so, all groups showed a dramatic need for improvement, with consumption of fruits, vegetables, and whole-grains falling far short of desirable levels. An increase in consumption of these foods would go a long way toward increasing the fiber and micronutrients in our diets, and reducing the amount of fat."

Because diet is estimated to contribute to 35 percent of all cancer deaths, NCI has developed a set of six dietary guidelines to reduce cancer risk. (Since the survey was completed prior to these guidelines, this study is not an evaluation of guideline adherence). The food intake study focused on foods that are addressed by three of the guidelines:

- Include a variety of fruits and vegetables in the daily diet.
- Increase dietary fiber intake to 20 to 30 grams a day, without exceeding 35 grams.
- Reduce daily fat intake to 30 percent or less of calories.

"Fruits and vegetables thought to be of special importance to cancer risk reduction are those rich in vitamins A and C," Patterson explained. "But about three-quarters of the study population failed to include a vitamin A- or vitamin C-rich fruit or vegetable in the day's diet." Examples are dark green leafy vegetables, citrus fruits, and yellow-orange fruits and vegetables.

Similarly, less than 20 percent of the population ate a cruciferous vegetable on the survey day. "Members of the cruciferous family, such as cabbage and greens, are thought to reduce cancer risk, and these low-cost vegetables are high in nutrients and low in calories," Patterson said. Other good examples are broccoli, cauliflower, turnips, and brussels sprouts.

Corn and dried peas and beans, relatively rich in fiber, were eaten by only 20 percent of adults. "Because so many Americans did not eat enough fruits and vegetables, and consumption of whole-grain breads and cereals was also low, daily fiber intake was only about 11 grams—well below the recommended 20 to 30 grams," Patterson said.

Some food choices relevant to fat intake were reported in this study. Fifty-five percent ate red meat, while poultry and fish were consumed by over 33 percent of the population. Also, more than 40 percent of the population ate at least one serving of lunch meat or bacon on the survey day. These foods have a high fat and salt content, and NCI recommends that people minimize consumption of salt-cured, nitrite-cured, smoked, and pickled foods.

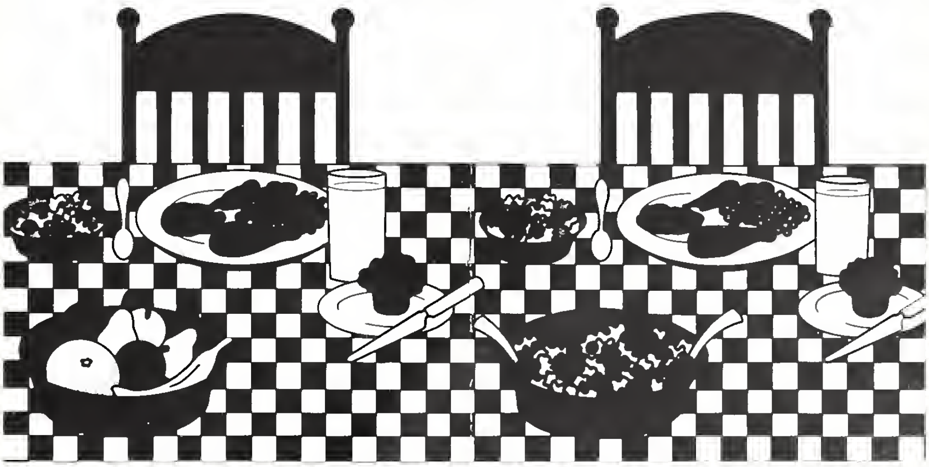
Looking at the data by race, the researchers found that blacks consumed more cruciferous vegetables and vegetables rich in vitamins A and C than whites, largely due to their greater consumption of greens such as collards. Fruit consumption was lower among blacks than whites. High-fiber cereals and whole-grain breads were more popular among whites than blacks. The survey covered data on 10,322 whites and 1,336 blacks.

Consumption of fruits and vegetables as well as red meat increased with income for both blacks and whites. High-fiber cereals and whole-grain breads, often more expensive than their low-fiber counterparts, were eaten more frequently by whites but not blacks as income increased.

Food intake varied by region. Poultry and fish were eaten by more people in the South and the Northeast than in the West and Midwest, for both blacks and whites. Red meat consumption was lowest in the South for blacks and whites. High-fiber cereal consumption was highest in the Northeast and West and lowest in the South.

Use of a 24-hour dietary survey focused on food choice rather than specific nutrient consumption. "Although one-day food records are not representative of an individual's usual intake," Block explained, "they do provide a picture of population consumption on a given day."

The researchers noted that factors such as the increase in salad bars and promotion of low-fat, high-fiber diets by various scientific and government agencies may cause changes in eating habits in certain segments of the American population. The NCI and USDA are continuing to study dietary consumption patterns in order to identify these and any other changes that may be occurring. ■



Estrogen Replacement Therapy Gets Approval from NIA Expert

Jan S. Ehrman

The benefits of estrogen replacement therapy (ERT) far exceed the potential dangers of taking the supplemental hormone for the majority of symptomatic, postmenopausal women. Statistically, "women taking oral estrogens have a much lower chance of dying prematurely than women who do not," says Dr. S. Mitchell Harman, Acting Chief, Endocrinology Section, Laboratory of Clinical Physiology, of the National Institute on Aging's Gerontology Research Center in Baltimore.

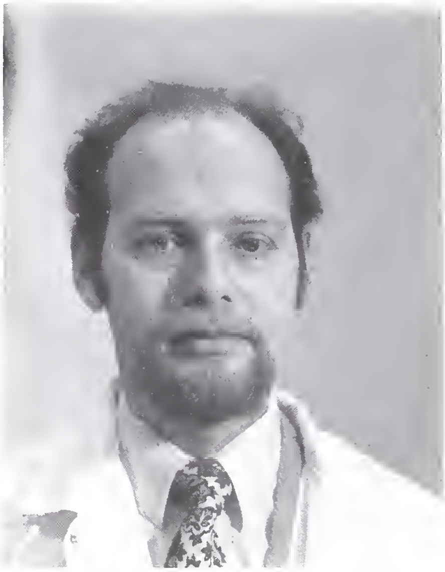
While he favors the use of estrogen replacement therapy, Dr. Harman states that not all experts agree that the benefits outweigh the risks, or that it should be widely prescribed.

Still, the question of whether or not to use oral estrogens to treat symptoms related to menopause *is* becoming less and less controversial as time goes on, according to the endocrinologist. "Our position really hasn't changed in the past four or five years," Dr. Harman said. Conjugated oral estrogens, when taken in a regimen that includes progesterone, provide numerous benefits in preserving a woman's health and well-being during mid-life and beyond, he believes.

He said that 60 percent of all women experience some symptoms during menopause, while 15 percent report disabling symptoms severe enough to impair day-to-day functioning.

The benefits of taking estrogen supplements are well documented. They can include reducing or preventing hot flashes, often one of the earliest and most pronounced symptoms of menopause; preventing vaginal atrophy, a condition that promotes alterations in vaginal flora, leading to chronic atrophic vaginitis (which responds only to estrogen); and possibly decreasing the risk of cardiovascular disease, although not all experts agree on this. The hormone may also improve sexual and psychological functioning.

But perhaps its best established usage lies in estrogen's ability to inhibit bone loss and ward off osteoporosis, a crippling disease with potentially devastating consequences. Due to estrogen deprivation brought on by menopause, women often lose excessive amounts of calcium from their bones. This can lead to fractures of the spine, hip, wrist, and long bones, and, in turn, may result in a poor clinical prognosis for the patient.



Dr. S. Mitchell Harman of the NIA's Gerontology Research Center in Baltimore, believes that the benefits of estrogen replacement therapy exceed the risks.

Oral estrogen appears more effective than calcium supplements in maintaining bone mass, Dr. Harman said. A number of well-controlled studies reveal that women taking estrogen supplements experience far fewer fractures than do untreated females.

Dr. Harman cited recent data indicating that there are 75 deaths (related to hip fractures) per 1000 untreated women and 30 hip-fracture related deaths for every 1000 women taking estrogen. This works out to be about a 60 percent "protection factor", he added, noting that the high incidence of morbidity from bone fractures should not be underestimated either.

Dr. Harman strongly emphasized the importance of adding a progestogen-like hormone to the estrogen replacement therapeutic regimen. Estrogen stimulates the growth of endometrial tissue, thus increasing a women's risk for developing endometrial carcinoma by 4 to 14 times the risk for untreated women. And while this form of cancer is highly curable when detected and treated early, progesterone can halt tissue growth and prevent this problem. Almost all estrogen-dependent women should follow this "opposed" therapy, which usually includes taking progesterone for 10–14 days out of the month along with the oral estrogen. Such therapy, like that with estrogen alone, requires monitoring, but the optimal monitoring program remains open to debate. Women taking estrogen alone will rarely experience vaginal bleeding (artificial periods), but nearly all women taking estrogen-progesterone will experience minor bleeding.

Hormonal therapy is not advisable for all menopausal and post-menopausal women. Patients with a prior history of breast carcinoma should *not* receive estrogens and women at high risk for developing coronary artery disease may need to be monitored closely if given progesterone. While estrogens improve lipid profiles, progesterone sometimes creates a negative effect by raising the LDLs or low-density lipoproteins (the "bad" cholesterol) and lowering HDLs, high-density lipoproteins (the "favorable" cholesterol).

According to Dr. Harman, what is needed is a way to optimize progesterone treatment for *all* women to ensure that they will not develop atherosclerotic disease. The progestogen most frequently prescribed, medroxy-progesterone acetate, appears to be the best choice, since this medication produces the least unfavorable effect on lipid levels.

New ways of administering hormone supplements are currently in use. The transdermal (skin) estrogen patches, for example, have their benefits and drawbacks. While they do not influence liver function (oral estrogens may), it remains unknown how they affect blood lipid levels and whether or not they can avert bone loss.

Another treatment, estrogen-progesterone implants, though experimental, appears promising and may someday be the ideal therapy for preventing or treating symptoms attributable to menopause. ■

Survey Reveals Current Public Practice on Screening, Smoking, Diet and Cancer

Cori Vanchieri

A first glimpse of what Americans know about controlling cancer and what they are doing to prevent cancer and to detect cancer early is provided in preliminary data from a supplement to the National Health Interview Survey (NHIS).

"Results show that Americans are not getting the necessary cancer screening tests to detect breast, cervical, and colon cancers," said Maryann Roper, M.D., acting deputy director of the National Cancer Institute (NCI).

The NHIS is an at-home interview conducted routinely by the National Center for Health Statistics (NCHS). In 1987, NCI collaborated with NCHS to add a half-hour questionnaire on cancer. The first-quarter data (covering January through March 1987) have been analyzed by researchers at NCI.

Other results show that smokeless tobacco use is way up, especially among young men; snuff use has more than dou bled for all ages since 1970; and about 68 percent of Americans believe there is a link between diet and cancer, although many are unsure of what to do about it.

"Although the numbers are only from the first quarter of 1987—covering one-fourth of the total 48,000 study participants, they give a strong indication of what Americans know about cancer control and what changes are being made to reduce cancer risk," said NCI's Benjamin Hankey, Sc.D., who developed the original concept and proposal for the supplemental questionnaire.

Following are some of the first-quarter results:

Cancer Screening Knowledge and Behavior

"The number of people who get cancer screening tests as often as recommended is much lower than we'd like to see," said NCI's Larry Kessler, Sc.D., lead analyst of the study. "Knowledge of the different screening tests is fragmented and poor."

Most of the 5,723 people who answered this part of the survey had heard of the screening tests, but confusion arose regarding how often to have the tests, Dr. Kessler explained. Up to 15 percent of those interviewed thought that mammograms, blood stool tests, and proctoscopy (insertion of a thin, lighted instrument into the rectum allowing a physician to view the lower part of the colon) were only needed for a problem.

"The point of screening is to catch disease early, before a problem is suspected, so that the chance of survival is greatest," Dr. Kessler noted.

When respondents were asked the main reason for *not* getting the tests, the top three replies were:

- no problems and therefore no need for the tests,
- putting it off, and
- the tests had not been recommended by their physicians.

Here are the results on the use of four common cancer screening tests:

Pap test. Almost 25 percent of the women 18 and older (excluding those who had had hysterectomies) had *not* had a Pap test within the past three years. NCI guidelines state that all women 18 or older or who are sexually active should have an annual Pap test to detect cervical abnormalities. After three or more consecutive negative tests, the Pap test may be performed less frequently at the discretion of the woman's physician.

Mammography. More than 60 percent of women 40 and older had never had a mammogram for early detection of breast cancer. According to NCI guidelines, these breast X-rays should be encouraged for women 40 and over every one to two years, and should be given annually starting at age 50. If women followed the screening guidelines, scientists estimate that breast cancer deaths would decline by at least 30 percent.

Blood stool tests and proctoscopy. More than 60 percent of men and women 40 and over had never had a blood stool test, and more than 70 percent had never had a proctoscopy. Starting at age 50, blood stool tests should be given annually, and proctoscopy exams should be given every three to five years. These tests are used to detect cancers of the rectum and colon.

Tobacco Use

Cigarettes

About 30 percent of Americans 18 and older smoke cigarettes, according to the 1987 first-quarter data. The highest percentage of smokers are black and low-income men. More men than women are heavy smokers (smoking 25 or more cigarettes per day), and more whites are heavy smokers than blacks. Prevalence of male smokers has declined from about 52 percent in 1965 to around 33 percent in 1987. The percentage of female smokers has declined from 34 percent in 1965 to 28 percent in 1987.

Most of the people who quit smoking had been light or moderate smokers, according to NCI's Gayle Boyd, Ph.D., coordinator of the tobacco use section of the questionnaire. The proportion of heavy smokers has changed very little since 1965. The NHIS data show that approximately 10 percent of men and 6 percent of women age 18 and older are heavy smokers. These smokers appear to have the most difficulty quitting smoking, and because their tobacco consumption is high, are at the greatest risk for developing smoking-related diseases.

About 30 percent of all cancer deaths are related to smoking.

Smoking in Public Places

The NHIS contains the first national data that have been made available regarding smokers' and nonsmokers' practices and attitudes about smoking in public.

When asked if people should smoke in public places where it might disturb others, 80 percent of all respondents said no. More than 60 percent of smokers agreed. But not quite a third of smokers will refrain from smoking in public. When a smoker lights up in public, the majority of nonsmokers surveyed said they would move away or do nothing. About five percent said they would ask a smoker to stop.

Smokeless Tobacco

"Use of smokeless tobacco has dramatically increased in the past 10 to 15 years," Dr. Boyd said. Young men (ages 18 to 29) have the highest rates of use; more than seven percent use some form of snuff or chewing tobacco. This practice is most common among young white men. Very few young black men have picked up the habit. This study showed no sign of a decrease in the use of smokeless tobacco among young men. Smokeless tobacco has been linked to cancers of the mouth and throat, gum disease, tooth loss, increased blood pressure, and oral leukoplakia (a precancerous condition), and it can lead to nicotine addiction.

The first-quarter tobacco use data covered 11,090 U.S. adults age 18 and older; 4,629 men and 6,461 women.

Nutrition Knowledge and Beliefs

About 68 percent of the 5,641 people questioned about diet believe there is a relationship between diet and cancer. Another 17 percent believe there is a link between diet and other diseases, but not diet and cancer. The remaining 15 percent of the survey population do not believe there is a link between diet and cancer or any other disease.

Researchers estimate that diet may contribute to 35 percent of all cancer deaths. Awareness of the diet-and-disease relationship increased with education and income, according to the first-quarter NHIS data, peaking at ages 35 to 44 and declining at older ages. "Although many American adults are generally aware of the diet-and-cancer message, they don't know how to act on it," said NCI's Barry Portnoy, Ph.D., an expert in health education.

A 60-item diet history questionnaire did show improvement in some food choices among those who believe there is a relationship between diet and disease. Their diets were higher in foods rich in fiber, carotene (a precursor of vitamin A), and vitamin C. "Increased consumption of these foods may reduce cancer risk," said NCI's Gladys Block, Ph.D., who designed the diet questionnaire.

The survey was a 30-minute, at-home interview covering a cross-section of the adult American population (ages 18 and older) with an oversampling of blacks and Hispanics. One adult in each home was interviewed at random.

"Along with providing useful information about what Americans are doing now to control cancer, the data will be coupled with a four- to five-year followup to provide feedback to help NCI develop and evaluate national cancer control programs," Dr. Roper said. ■

Building a Better Bacterium: How a Newly Discovered Genetic Marker May Lead to Improved Antibiotics

Anne A. Oplinger

The advent of large-scale antibiotic production in the mid-1940's was a dramatic medical advance. Physicians, who had been helpless when faced with patients who had such bacterial infections as scarlet fever, pneumonia, meningitis, and bacterial endocarditis, were given a powerful new weapon against these diseases in the form of penicillin, the first of the new "miracle drugs."

Penicillin, which is produced by *Penicillium* molds, destroys bacteria by interrupting the manufacture of their cell walls. Another widely used antibiotic, streptomycin, is derived from soil-dwelling microorganisms of the genus *Streptomyces*, and works by disrupting protein synthesis in disease-causing bacteria.

In nature, microorganisms are assumed to use antibiotics to drive off competing bacteria. Antibiotics are produced through a complex series of enzymatic steps during certain phases of a microorganism's life cycle, and are called secondary metabolites because they do not appear to be essential to the growth of the organism. More than 5,000 antibiotic substances are found in nature, and about 300 more are discovered each year. Nevertheless, because disease-causing bacteria can become resistant to antibiotics, scientists must continue to search for new, more effective antibiotics and to improve existing ones.

Chemical modification (or semi-synthesis) is a time-honored method of improving the therapeutic properties of naturally occurring antibiotic molecules. Scientists can also make novel antibiotics by deliberately mutating large numbers of organisms, and then searching for the mutants whose altered genetic structure enables them to produce better antibiotics. Both of these methods, successful as they have been, are laborious and costly. In recent years, advances in microbial genetics have made it possible to begin to rearrange antibiotic production genes in the laboratory so that the organisms themselves make better antibiotics. This rational means for antibiotic development probably will be cheaper in the long run than randomly mutating bacteria, says C. Richard Hutchinson, Ph.D., a professor of medicinal chemistry and bacteriology at the University of Wisconsin, Madison, and a grantee of the National Institute of General Medical Sciences (NIGMS).

Before a bacterium's antibiotic-producing abilities can be improved, however, the genes that code for antibiotic manufacture must first be located among all of the organism's genes. This is a lengthy and difficult task, but recently Dr. Hutchinson and his colleagues, in collaboration with British researchers, discovered a "marker" gene in two antibiotic-producing organisms that can be used to detect the sought-after antibiotic genes in many other organisms. "The discovery of this marker will significantly change the way antibiotic research is done," says Dr. Hutchinson. "Now it will take months, instead of years, to locate genes we are interested in that control drug production in bacteria."

Dr. Hutchinson and his colleagues determined the sequence of subunits in the marker gene, which allowed them to construct an identical piece of DNA in the lab. They then used this piece of DNA as a "probe." When applied to the total DNA of a strain of bacteria, the probe seeks out and binds to the part of the bacterial DNA that has a complementary sequence, thus alerting the researchers to the presence of a gene involved in antibiotic production.

The marker gene that Dr. Hutchinson and his colleagues have identified is particularly useful since it attaches itself to the polyketide genes. Polyketides are an important early intermediary in antibiotic production in many organisms, and so a gene that codes for a polyketide is found in a wide variety of antibiotic-producing bacteria. Moreover, because the genes involved in other steps of antibiotic production tend to be clustered in a bacterium's chromosome, the polyketide marker helps researchers locate an entire group of antibiotic genes.

The work that led to the identification of the polyketide marker gene was funded by the National Cancer Institute. Dr. Hutchinson also has received NIGMS support for a number of years for complementary studies to investigate both the genetics of antibiotic production and the chemical structure of polyketide antibiotics. NIGMS is now supporting his use of the new marker to search many kinds of bacteria for their antibiotic-producing potential. The marker, he says, has given him the capacity to clone potential antibiotic production genes that he would not otherwise have been able to find.

Eventually, Dr. Hutchinson says, researchers hope to locate the one or two pieces of bacterial DNA that are believed to control all antibiotic production. If this can be done, it may then be possible to systematically rearrange a bacterium's genes so that it produces more or better antibiotics. ■

Cancer Nurses Play an Important Role in Research

Francis X. Mahaney, Jr.

When Karen Montrella was 15 years old, she says she felt "so angry" at the way nurses treated her in a Philadelphia children's hospital, she vowed she would never become a nurse.

Now, 10 years later, she is a pediatric nurse at the National Cancer Institute (NCI) in Bethesda, Md., and cancer nursing has become "the ultimate challenge" of her "heart and her head."

"To be a pediatric nurse you have to love kids," the 25-year-old registered nurse says. "But cancer nursing is an even greater challenge of the heart. I became a cancer nurse because I wanted to find new ways to alleviate the pain in these young people and turn their lives around."

Marcie Sheler is one of her patients on 13 West, a ward at the National Institutes of Health (NIH) Clinical Center where cancer patients are treated by NCI doctors. Marcie has acute lymphocytic leukemia, a cancer of the body's blood-forming cells. In many ways, she reminds Nurse Montrella of herself. Marcie is 15.

Two years ago, when Marcie was diagnosed, she found herself angry and frustrated, as she struggled to achieve order from the confusion that surrounded her. But Montrella was with her "all along the way," through the pain and chemotherapy, Marcie says.

Montrella even took time off to speak to Marcie's high school teachers and friends about her disease.

"When I first found out I had cancer, life came to a complete halt," Marcie says. "But now that I am getting better, Karen has shown me so many things to look forward to, that there is hope and I can move on."

For Marcie and the nearly one million Americans who will be diagnosed with cancer this year, cancer is an intense personal battle, as well as one that requires a high degree of medical knowledge, skill, stamina, and compassion from care providers.

At NCI, the goal of nursing care is to give each person the best chance for a cure and the highest quality of life while they are here. But oncology nursing is more than just care-giving at NCI. The nurses play a hands-on role in the nation's cancer research.

Each year, some 34,630 cancer patients come for treatment at the NIH Clinical Center, some for studies lasting for a few days, others for many months. The clinical center is also the main treatment center for 10 other NIH institutes.

A total of about 9,000 patients a year are admitted to the 500-bed clinical center for hospital treatment, and another 145,000 outpatient visits are logged in yearly. In addition, there are more than 1,000 laboratories within the facility conducting clinical research.

NCI nurses like Montrella carry out complicated research on childhood and adult cancers and on AIDS. In the last year alone, NCI nurses participated in about 140 treatment studies on cancer.

"Nurses at NCI do more than just hand out bedpans and bathrobes," says 37-year nursing veteran Rose Thomas. "Nursing has grown," she says, "from being a task-oriented profession of taking vital signs and handing out prescriptions, to doing research pharmacology on new anticancer drugs, and contributing to better primary patient care."

Thomas is involved in clinical studies to treat AIDS. She cares about both the personal welfare of her patients and the scientific inquiry, meticulously testing new drugs for their ability to inhibit the AIDS virus and checking them for possible harmful side effects.

Her research has contributed to the first AIDS drug to be approved by the Food and Drug Administration—azidothymidine (AZT). It is now widely used around the world. Thomas recently co-authored a major study in the British medical journal *The Lancet* announcing the first data on the antiviral effects of AZT in combination with dideoxycytidine in treating AIDS patients. "I don't think there is a single hospital in the country or the world that allows a nurse as much creativity as NCI," Thomas says.

But research nurses such as these are often asked: "Isn't working with terminally ill patients depressing?"

"It can be at times," says Pat Duffey, who has been an oncology nurse for 10 years, "but it can also be extremely rewarding to follow with a patient step by step, from diagnosis through treatment and after, knowing regardless of treatment outcome, that the patient has had the best opportunity for possible cure." Duffey, who for the past several years has seen more than 500 cancer patients on eight NCI projects, is currently administering an investigational drug regimen called "short course ProMACE-CytaBOM" to adult patients with lymphomas—cancers of the immune system.

"Life is very fragile. But I enjoy working with these patients in situations where consistency and attention to all details of care can make a tremendous difference in the outcome for each patient as well as the overall outcome for the research study."

Nursing research has come a long way since the turn of the century. In the early 1900s, there were scarcely 50 or so articles devoted solely to nursing. From 1900 to 1930, there were only 16 professional nursing articles written about cancer, and only two of these were actually written by nurses.

Today, there are more than 493 nursing journals, the National Library of Medicine reports. Nearly all of the 33,947 articles written from January 1987 through January 1988 were authored by registered nurses.

Because, by necessity, nurses spend more time with hospitalized patients than physicians are able to, nurses have become innovators in clinical care, inventing new devices, even advising physicians when and how to give new medications, says Jean Jenkins, R.N., special assistant for clinical affairs in NCI's Medicine Branch.

Even medical emergencies are often spotted first by nurses on the ward. Margaret Cudd, a 74-year-old retired nurse, found out she had ovarian cancer 12 years ago. One night at home, when Cudd was not feeling well, she called Jenkins for advice. Jenkins deduced that Cudd had sepsis, a deadly infection of the blood and paved the way for her to be admitted to a hospital and thus helped save her life.

It is medical emergencies like this that have pressed nurses to become more educated than their peers a decade ago.

More than 60,000 of the 1.9 million registered nurses in this country specialize in cancer treatment and care, according to the Oncology Nursing Society (ONS).

As medicine becomes increasingly more complex, many nursing professionals are pushing states to require baccalaureate degrees for nursing certificates, replacing the hodgepodge of two- and three-year programs. Presently about 40 percent of the more than 12,000 nurses in the Oncology Nursing Association have baccalaureate degree. Another 24 percent have masters degrees or above, a recent ONS study indicates.

And yet, a critical nursing shortage in this country is "seriously slowing down scientific research," says Bruce Chabner, M.D., director of NCI's Division of Cancer Treatment.

Because of the shortage, NIH has implemented a major nursing recruitment program. Under a new law that places employees of the NIH Clinical Center on the same pay scales as employees of the Veterans Administration Hospitals, NCI nurses received large salary increases this year, says Kathleen M. Thaney, chief of the Cancer Nursing Service.

Entry level salaries range from $26,838 to $30,547. Advanced nursing staff salaries can range as high as $40,652, making the NIH nursing salaries competitive in the Washington-Baltimore area.

Meantime, Thaney says, the Cancer Nursing Service is encouraging nurse training with free tuition programs leading to advanced degrees, internships for recent nurse graduates, support groups designed to prevent nursing burnout, and internal promotion potential for staff nurses via a career ladder. This ladder rewards bedside nursing expertise and encourages professional growth—all important nursing retention factors. Also, according to Thaney, the NCI recently hired psychiatric nurse Jacques Bolles, R.N., to work with nurses and patients.

Still there are others that say they would work in cancer nursing at any cost. Pat Duffey, for example, has recently co-authored a chapter with two other nurses in a leading medical textbook on cancer, *Cancer: Principles and Practice of Oncology.*

Nurse Montrella is hard at work on a series of children's books for cancer patients. Her first, *Spaceship Friendship*, which will be published this year, will be a space exploration which describes the journeys that cancer cells and other cells take. ■

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Special Issue: Animals in Biomedical Research

NEWS & FEATURES
from NIH

May/June 1990

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Animals in research are not only the providers of valuable information, they are sometimes the beneficiaries as well. For example, NCI scientists—working with a team of scientists at the National Zoo—are studying the biology of endangered species in an effort to develop new strategies for preserving these species. An endangered animal of interest is the cheetah—the fastest mammal on land—with fewer than 15,000 survivors and a genetic history that may provide clues to its future survival. See page **5.**

Basic research using animal models, such as the roundworm, fruit fly and mouse, has yielded important information on cell specialization and gene expression and control. Some of this work—supported by the NIGMS—may provide additional understanding of certain human diseases and have eventual application to gene therapy. See page **11.**

Animal Research: Perception and Reality

During the past decade, antivivisectionism has reappeared under the unfurled banner of the "animal rights" movement.

In spite of the fact that virtually all major medical advances in the past century have depended, in one way or another, on animal research, leaders in the "rights" movement are advocating the elimination of research involving laboratory animals.

These leaders have orchestrated pressures on the Congress and the Executive Branch designed to produce severe restrictions that could impede, and ultimately destroy, the Nation's effort in biomedical research. In addition, tactics employed by extremists of the movement have included theft of experimental animals, destruction of property, death threats, and other lawlessness with a view toward intimidating scientists and increasing the costs of animal experimentation.

Numerous stories have appeared in the press, and spokespersons for the movement have appeared on radio and television. Some of the themes running through these presentations give the misleading impression, if not the explicit falsehood, that animal research *per se* is unnecessary, is cruel and is wasting Federal taxpayer dollars. These presentations promote the perception that something is wrong, and frequently they point an accusatory finger at the National Institutes of Health (NIH) and its awardee institutions.

What is the reality?

NIH, one of the agencies of the Public Health Service (PHS), is the primary biomedical research agency in the Federal Government. Its mission is to improve the health of the American people through research. The use of animals has been an integral part of the Federal Government's medical research effort for more than a century and will need to continue indefinitely if the NIH mission is to be fulfilled.

The litany of research accomplishments based on animal research since World War II is testament to its value and necessity. Polio vaccines have eliminated infantile paralysis in this country. Coronary bypass operations and transplantation of hearts, lungs, kidneys, and livers have extended the lives of thousands. An array of drugs has reduced mortality rates attributed to stroke and a variety of cancers; the stroke mortality rate has declined 58% in the past 20 years. About 50% of all cancer patients can expect to live free of the disease for at least five years, and about 75% of children with some of the once-dreaded forms of leukemia will recover. These illustrate a few of the areas where animal research has made a dramatic and indispensable contribution toward preventing or curing disease. This special issue of *News and Features from NIH* includes several areas of current research where animals play a key role.

Since 1963, the Public Health Service has led the way with detailed guidelines on humane care and use of laboratory animals. All awardee institutions have an institutional animal care and use committee and give written assurances that they will abide by the regulations of the PHS, and the Animal Welfare Act (administered by the U.S. Department of Agriculture), as well as state laws and local ordinances. When grant applications for research involving animals reach the NIH, an initial peer review group critiques the appropriateness of the species and number of animals proposed; the plans for the care of the animals before, during, and after experimental procedures, and other information that has significance for the treatment of animals. No award of NIH funds can be made unless all issues have been resolved to the satisfaction of the NIH. Similar procedures are applicable to contract-funded and intramural projects.

During the past decade, NIH's Office for Protection from Research Risks conducted 86 inquiries and investigations into alleged non-compliance with the PHS animal welfare policy. For many of these, the allegations or concerns proved unfounded. For others, remedial steps were prescribed and quickly implemented. In 13 instances OPRR's staff found deficiencies that required punitive action ranging from reprimands to suspension and/or loss of NIH funds for animal research.

NIH supports more than 16,000 projects involving animals at approximately 800 awardee institutions. These institutions have been the front-line players in our successful efforts to ensure proper care and use of laboratory animals. We at the NIH believe that, with very few exceptions, our trust in these institutions has been well placed.

In short, the NIH has been vigilant to balance two imperatives: to improve the health of Americans and to provide for proper care and use of animals involved in biomedical research. We and our awardees know that good animal care is an essential part of good science. And, everyday we are guided by the conviction that the quest to improve human health through research, including animal experimentation, is one of the noblest callings of our civilization.

William F. Raub, Ph.D.
Acting Director, NIH

Sam the hamster looks brightly out at the laboratory world which surrounds him and of which he is so much a part. He is an example of the countless thousands of small laboratory animals—rats, mice, guinea pigs and hamsters—whose services have been and will continue to be important aids in the advance of man's knowledge of life processes. This photograph ties in with no particular research accomplishment, but is presented merely as a rather interesting photograph and as a salute to all the laboratory animals who have in the past and will in the future help the world's health scientists in their search for knowledge with which to fight disease and build toward a healthier world in which to live.

Courtesy of NIH Feature Service, March 1971.

New Dog-Tested Preservative Improves Transplantation

Charlotte Armstrong

A new preservative first tested in dogs has tripled the length of time the pancreas and liver can be stored viably before transplantation. Success rates of liver transplants are higher with the new solution, and the extra time it provides—30 hours as compared with 8 with previous technology—increases organ availability and gives medical staff greater leeway to schedule surgery and prepare the patient.

The preservative, developed at the University of Wisconsin and named the "UW solution," adds to the many advances in transplant and other surgery made possible only because of research on large mammals such as dogs. These large animals, which anatomically resemble humans, provide a better model for testing surgical methods than smaller animals such as rodents.

The number of liver and pancreas transplants has been increasing thanks in part to new drugs that suppress rejection. Earlier methods of organ preservation have severely limited the distance over which donor livers and pancreases could be transported, effectively limiting the supply of these organs. Candidates for transplants had to remain at or near the hospital, so emergency surgery could be scheduled as soon as a donor organ became available.

To solve these problems, University of Wisconsin scientists Dr. Folkert Belzer and Dr. James Southard and colleagues developed the new preservative solution with grant support from the National Institute of Diabetes and Digestive and Kidney Diseases, using components developed by Du Pont Pharmaceuticals. Once an organ is removed from a donor, it must be kept cold and bathed in a solution that prevents cells from absorbing water and swelling. The University of Wisconsin scientists looked for chemicals that limit water absorption in preserved organs and that also prevent injury from chemical changes that occur in organs deprived of a blood supply.

In order to test a new preservative solution, the scientists needed an animal model that physiologically resembles humans. Rodents are unsuitable because of differences in their metabolism and immune systems. Rodent organs are more difficult to preserve than human organs, and their small blood vessels greatly complicate transplant surgery. These animals, for example, do not survive having their blood bypassed to a heart-lung machine, so heart transplant surgery is impossible.

The University of Wisconsin scientists tested the UW solution by transplanting organs in dogs. The alternative would have been "blind" testing of the technique in human surgical patients. To avoid unnecessary hazards to patients, the Food and Drug Administration (FDA) requires data from testing in large animals before the agency considers approving agents like UW solution for testing in human patients.

Experience with the UW solution in transplantation in animals led to clinical trials. The successful results of trials at the University of Pittsburgh, a leading transplant center, were reported by Drs. Satoru Todo and Thomas Starzl and colleagues in the February 3, 1989 issue of *Journal of the American Medical Association*: "The remarkable effectiveness of the solution has revolutionized liver transplantation at almost every level. The enhanced margin of safety has permitted more effective use of organs that can be stored safely while waiting for operating room facilities or personnel to become available."

In research on transplant surgery at the University of Wisconsin, this animal received its own kidney back after the organ had been removed and preserved.

The UW solution has made possible transplants of organs shipped across the United States and even across the Atlantic. The FDA recently approved UW solution, whose trade name is ViaSpan™, for marketing. Preliminary research shows that the solution may also be effective in preserving heart tissue.

Liver transplantations are performed for a variety of conditions in both adults and children. There is no equivalent to kidney dialysis for someone whose liver is not functioning normally, so liver transplantation is a life-saving operation.

Pancreas transplantations are performed in people whose own pancreas has been removed, or who have insulin-dependent diabetes (IDDM). People with IDDM must have injections every day to replace the insulin their own pancreas does not make. Despite daily insulin injections, long-term complications of diabetes can be life-threatening. However, the pancreas transplant, if successful, gives the body needed insulin more naturally than periodic injections. Many diabetes experts believe the development of complications is related to how closely insulin replacement resembles the normal production of insulin.

Research in dogs may one day free patients with diabetes from insulin injections—a treatment that has saved thousands of lives since its discovery in the 1920's through research using dogs.■

Surgeons at the University of Wisconsin carefully place a donor liver in a bag containing Du Pont Pharmaceutical's ViaSpan™, a new organ preservation solution cleared for market by the FDA. ViaSpan™ can triple the time between the donation of a liver or pancreas and its transplantation into a recipient.

CONTACTS: Roger Morris or Gordon Heidelberg
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Monkey Model Offers Therapeutic Promise in Parkinson's Disease

Louise Williams

For some Americans, no golden retirement years await. Instead, they face the shrinking horizons and greater hardship of Parkinson's disease, a neurological disorder that cuts the tie between thought and movement, leaving its sufferers without muscular control.

Until recently, Parkinson's was difficult to study because it apparently affects only humans. However, a rash of accidental self-inflicted poisonings by drug addicts in the late 1970s and early 1980s gave scientists a clue for duplicating Parkinson's symptoms in an animal model.

The National Institute of Neurological Disorders and Stroke (NINDS) is a world leader in research on Parkinson's as well as on other brain and central nervous system disorders. The NINDS coordinates the Federal Government's research on Parkinson's, a multimillion-dollar effort conducted at the Institute's own facilities in Bethesda, MD, and at universities and medical institutions worldwide.

Intramural studies, for instance, range from clinical drug trails to tests of the ability of brain-imaging techniques to "see" Parkinson's progressive destruction.

Perhaps most extraordinary are preliminary studies that suggest the brain may be able to at least partly repair itself, if properly stimulated. Not long ago, such a possibility seemed fantastic. Now, as studies yield ever more insights, hope is rising that a treatment will be found to stop or even reverse the harrowing decline of Parkinson's victims.

Targeting Cells

Approximately 500,000 Americans suffer from Parkinson's which usually strikes persons in their late fifties. Hence, its early symptoms of shakiness and decreased agility often are mistaken for commonplace signs of aging.

Eventually, however, loss of motor control causes tremors, an expressionless face, and difficulty walking. In time, the inability to initiate movement produces frozen states or akinesia. Swallowing becomes harder and, finally, bed rest is necessary. The decline may last for 20 years, with death resulting from a secondary complication, such as pneumonia.

While advances have been made in treating Parkinson's, the results have been mixed. For instance, Parkinson's major treatment grew out of a discovery 30 years ago that the disease results from the death of specific brain cells—those producing the neurotransmitting chemical dopamine, which relays impulses between nerves.

Unfortunately, dopamine cannot be infused directly into the brain to compensate for lost neurons. The brain sits within an insulating barrier, which restricts the bloodstream circulation of chemicals that might upset its delicate functioning. Dopamine is one such compound; it cannot cross the blood/brain barrier.

Monkey with Parkinson's symptoms uses only one limb to feed.

In the 1960s, scientists found a drug, levodopa, which can be transported across the barrier and into the brain, where it undergoes a chemical transformation into dopamine. But levodopa does not always work and can lose effectiveness after several years. It also does not halt the progressive nerve cell death characteristic of Parkinson's disease.

Because of these problems, scientists began seeking ways to spur the brain's own production of dopamine. And here, accident and misfortune turned to promise.

Recreating Parkinson's

It was known that Parkinson's neither afflicted animals naturally nor could be mimicked artificially, thus thwarting attempts to trace its etiology. Its exclusiveness seemed to lie in the particular portion of the brain devastated.

The region includes the substantia nigra, believed responsible for adjusting nerve signals passed outward to muscles from the brain's command centers. The term substantia nigra means black substance, referring to the dark pigmentation of the area's cells. These pigmented cells generate dopamine for nerves throughout the brain. No other species has as much black pigment as humans.

Then a decade ago, accidental self-inflicted poisonings of drug addicts gave investigators a possible lead. The addicts had made synthetic drugs, contaminated by a compound called MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a narcotic belonging to the demerol family.

The poisonings severely damaged the users' brains, bringing on severe motor disability and even total immobility. While users displayed classic symptoms of advanced Parkinson's, most were too young, some in their twenties, to have acquired the disease naturally and so suddenly.

Scientists soon traced the damage to MPTP. Analysis revealed that MPTP itself is not toxic. However, in the brain, it converts to another compound, known as MPP-plus (1-methyl-4-phenyl-pyridinium). Apparently this compound accumulates until it interferes with the function of cell mitochondria miniature power plants that convert energy into a usable form. Without life-sustaining energy, cells die.

Other mechanisms also may kill cells. MPP-plus produces harmful substances called free radicals. Many types of free radicals exist throughout the body, which usually protects itself against them. Scientists suspect that an MPTP-free radical connection may somehow evade those safeguards and destroy cells. It may be that the free radicals involved in Parkinson's harm cell mitochondria, perhaps robbing them o oxygen and causing cells to die.

Initially, scientists injected MPTP into rats, trying to induce parkinsonism. Their attempt failed, probably because the rat's brain lacks enough black pigmented cells to product an MPTP effect.

The investigators succeeded with primates, particularly monkeys, whose brains are second only to humans' in the amount of black pigmentation contained in the substantia nigra. Given MPTP, the monkeys display human-like pathological degeneration of dopamine-containing neurons.

Opening New Doors

The MPTP model has put scientists at a new threshold of research. The reasons are many: MPTP's effects appear quickly; the chemical can target one side of the animal's brain, leaving the other normal for comparison; and symptoms reverse rapidly with levodopa treatment. Also, MPTP causes clearly identifiable changes in activity, including circling toward the immobilized side and losing use of an affected arm.

The monkey model already has boosted the hunt for new therapies. In particular, it shows that the brain may be induced to make added dopamine, rather they relying

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on such drugs as levodopa. One way is via tissue implantation.

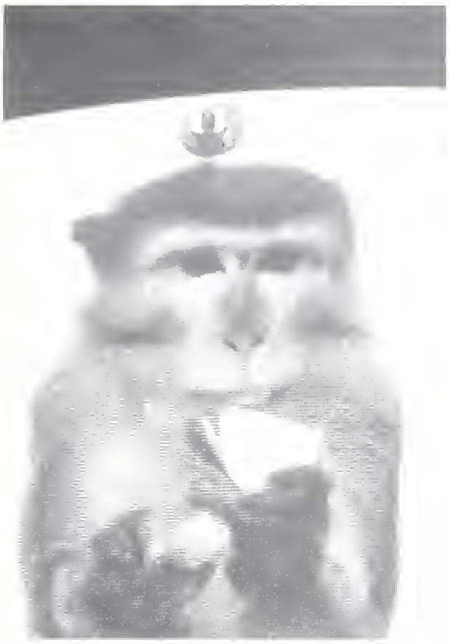
Several forms of implantation are under investigation. For example, NINDS intramural scientists, grantees at the Yale University School of Medicine in New Haven, Connecticut, and grantees at the University of Rochester School of Medicine in New York, produced dramatic recoveries in MPTP monkeys implanted with monkey fetal tissue. The implanted fetal tissue survived, grew, and apparently produced dopamine in the monkeys' brains.

Drs. Krzysztof Bankiewicz and Robert Plunkett of the NINDS's Surgical Neurology Branch found MPTP monkeys improved more from fetal implants than grafts of their own adrenal tissue, which gradually dies after implantation. In one study, animals with fetal implants showed stable improvement over 7 months, while those with adrenal grafts recovered less.

Intriguingly, the team also discovered that preparing a cavity site stimulates dopamine production. Surviving host neurons near such sites grew new fibers toward the cavity and may supply dopamine.

Implants of tissue from the amnion, the sac surrounding the fetus, produced recoveries similar to those from the fetal implants—yet amnion grafts contain no dopamine-producing tissue.

Such results indicate that the act of implanting may stimulate residual cells to sprout and produce dopamine. Possibly, the whole brain is repairing itself, with surviving cells trying to take over the functions of those killed by the neurotoxin.



Monkey after receiving a monkey fetal tissue implant uses both limbs.

Some day, scientists may devise a way of furthering the brain's struggle to make the most of its remaining neurons and heal itself.

Answering Why

As America's population ages, ever more cases of Parkinson's will occur. Only by finding out why Parkinson's develops can it be vanquished. Here too, the MPTP monkey may hand us the answer.

This list of Parkinson's possible causes includes environmental poisons and dietary toxins. For instance, MPP-plus resembles paraquat, an antifoliant, which also may produce free radicals.

Yet, such poisons seem unlikely candidates, partly because Parkinson's apparently predates the industrial revolution and thus most pollutants in air or food. In fact, the disease bears the name of Dr. James Parkinson, who first detailed its features in an 1817 publication.

However, contaminants may be just one genesis of the disease—a byproduct of modern life. So, scientists are testing whether neurotoxic cousins of MPTP produce Parkinson's.

As more work evolves with the MPTP model, other leads will be found. The MPTP model is supplying extraordinary clues to Parkinson's etiology, especially its destruction of certain neurons. Before the model's discovery, research inched stiffly forward; now, it moves steadily ahead. ■

Endangered Species Benefit from Research

Frances Taylor

Geneticist Stephen J. O'Brien believes animal research is a two-way street.

Advanced technology developed to benefit human health can aid animals as well says Dr. O'Brien, whose interest in the role viruses play in causing cancer brought him to NIH in 1971 as a staff fellow. He is now chief of the National Cancer Institute's (NCI) Laboratory of Viral Carcinogenesis in Frederick, MD.

"For a hundred years we've been studying animals to understand human biology," he said in a recent interview. "Most of the effort at NIH and in the scientific community goes toward understanding human biology.

"But there's a lot we can learn if we go the other way too—about both the animals and ourselves."

O'Brien has been going the other way since 1981 when he joined a team of scientists at the National Zoological Park working to unravel a problem in zoos: the poor breeding and endangered survival of captive cheetahs.

The cheetah, the fastest mammal on land, once roamed the globe. Now it is endangered, with 15,000 or fewer surviving wild in small scattered pockets of Africa.

In an attempt to increase the faltering numbers, breeders imported more than two hundred cheetahs into the United States in recent years. But only about 15 percent bred successfully. And too many of the few baby cheetahs produced died soon after birth.

The breeders were puzzled because other big cats are far more prolific. "Lions and tigers are some of the best breeders in the zoo today," O'Brien explained. "They breed like rabbits."

So, in 1982, O'Brien was called in to analyze the genetic structure of a cheetah population in South Africa.

Using molecular techniques on blood and skin samples he had employed since the 70's, he found that the cheetah has a profound lack of genetic diversity. "In most species somewhere between 20 and 40 percent of the genes show normal genetic variations, just like hair color and eye color.

"But when we looked at the cheetah we found none," he stressed. "The cheetah looked like it has been deliberately inbred."

O'Brien said the most "dramatic" example of the cheetah's lack of diversity came

Skin grafts on cheetahs, such as the one Dr. Stephen O'Brien performs here at the Wildlife Safari Park in Oregon, have helped demonstrate the cheetah's lack of genetic diversity.

when he and his colleagues attempted to show variation at the cheetah's major histocompatibility complex (MHC), a group of genes that enables the body to distinguish between foreign invaders and its own cells. Using the same type of skin graft techniques developed to treat human burn victims, they exchanged patches of skin between unrelated cheetahs.

"Normally," O'Brien said, "when you exchange a skin graft between unrelated individuals, be it humans, mice or pigs, you get a rejection of the foreign graft, usually within about 12 days. It darkens, hardens, thickens, and then it falls off." But in the cheetahs' case, all 14 grafts were accepted.

"The cheetahs were so inbred, they were so genetically uniform, that they actually share identical types at the MHC. It was as if they were all identical twins."

O'Brien and his colleagues theorized that the cheetah had gone through a severe population bottleneck, where the number of cheetahs had dropped to just a few animals, and close relatives were forced to breed. This would explain why unrelated cheetahs are so alike.

Such a lack of genetic diversity can make any species particularly vulnerable, O'Brien said, "because genetic diversity is somewhat like a moving target for pathological microbes that periodically afflict populations." For example, if some members of a species are resistant to a particular virus strain, then they can survive an epidemic and pass this resistance on to their offspring. But if all members of a species have identical disease resistance, then a virus that has evolved to cause disease in one individual would wreck havoc on the genetically homogenous population.

In fact, a similar epidemic occurred in cheetahs in 1982, soon after O'Brien had noticed their lack of genetic diversity. Two cheetahs that looked healthy were added to the collection of 50 cheetahs at a wildlife park in Oregon. However, the newcomers soon developed symptoms of feline infectious peritonitis (FIP), a disease that also occurs in domestic cats. While FIP usually kills about one percent of infected domestic cats, nearly 60 percent of the cheetahs died in this epidemic within three years.

"It was as if a virus came along and found an individual cheetah whose defenses it could overcome and looked around the park and saw that they were all the same," O'Brien recalled. "The virus ran through the colony like a train through a station."

Since then, three similar epidemics have occurred in other cheetah populations. Moreover, O'Brien and his colleagues have discovered that other species have little genetic diversity, such as the Florida panther and Asian lion.

O'Brien says these research findings "are not necessarily a death sentence for the cheetah." Instead, he says they have furnished information that can be used to increase the chances of survival for cheetahs and other endangered species. "Since we've done this work, I think that the conservation community has opened its eyes to the fact that things are happening to natural populations of animals that cannot be detected with a pair of binoculars."

O'Brien plans to continue animal research that supplements ecological field studies with biotechnology. Toward this end he serves as NCI liaison to the New Opportunities in Animal Health Sciences (NOAHS) Center. NOAHS was established in 1986 to raise and disburse private funding for the National Zoological Park's biomedical research on behalf of endangered wildlife species. (See story on page 7.)

"We are providing critical baseline data about the biology of endangered populations by taking advantage of the explosion in biotechnology that's been going on in the medical and research communities for the last twenty years. And we often can factor this knowledge into management strategy."

For example, other work by O'Brien's group using support from NOAHS Center has revealed a subspecies of cheetah in East Africa that has some genetic differences from other cheetahs. So zoologists armed with this knowledge can breed cheetahs from the two groups to restore some of the cheetah's diversity. In fact, O'Brien said, "Such a wildlife breeding program has already succeeded at the London Zoo where they have actually diminished their frequency of juvenile mortality."

O'Brien says that multidisciplinary research using genetics, reproductive physiology, clinical medicine, and screening for infectious agents are the tools of the future for preserving threatened species. "We now can assess the microbial risks in certain of these populations and make sure at least the captive populations are vaccinated when vaccines become available."

Most importantly, O'Brien said, basic research enables conservationists to separate good strategies for preserving these species from less appropriate ideas based on guesswork. "We can formulate a lot of new ideas when we have the data. But if we don't have the data, the ideas don't have any basis.

"The more we know about these populations and these species," O'Brien stressed, "the better equipped we are to reconstruct their past and influence their future."■

See The Cheetah on page 8.

Dr. Stephen O'Brien holds a member of the cat colony used for reproductive, immunologic, and genetic studies of the domestic cat at the NIH Animal Center in Poolesville, MD.

Photos used in this story courtesy of Dr. Stephen O'Brien, NCI.

They Build Arks at NOAHS Center

Sandra D. Levine

Noah's Ark lives on in the form of the Center for New Opportunities in Animal Health Sciences (NOAHS). This modern-day ark, with Director Laurie Marker-Kraus at the helm, was built to save species in danger of disappearing from the earth, through a combination of laboratory, zoo, and field research.

Created in 1986 as a part of the Smithsonian Institution's National Zoological Park in Washington, D.C., the Center supports and collaborates in research involving genetic, reproductive and veterinary medicine at the National Zoo and more than 25 other zoos and wildlife parks throughout the world.

NOAHS' research programs are based on studies begun in 1981 on cheetah reproduction and genetics by Drs. Stephen O'Brien (see main story), David Wildt, the Zoo's chief reproductive physiologist, and Mitchell Bush, the Zoo's chief veterinarian. Cheetah expert Laurie Marker-Kraus joined the team in 1983.

NOAHS continues to maintain strong ties with NIH. One of its "ark-itects," Stephen O'Brien, is at the NCI in Frederick, MD. O'Brien directs a research and training program that applies current biotechnologies of human genetics and molecular biology to field studies of the African lion, Florida panther, black-footed ferret, Giant panda, and humpback whale, as well as to humans.

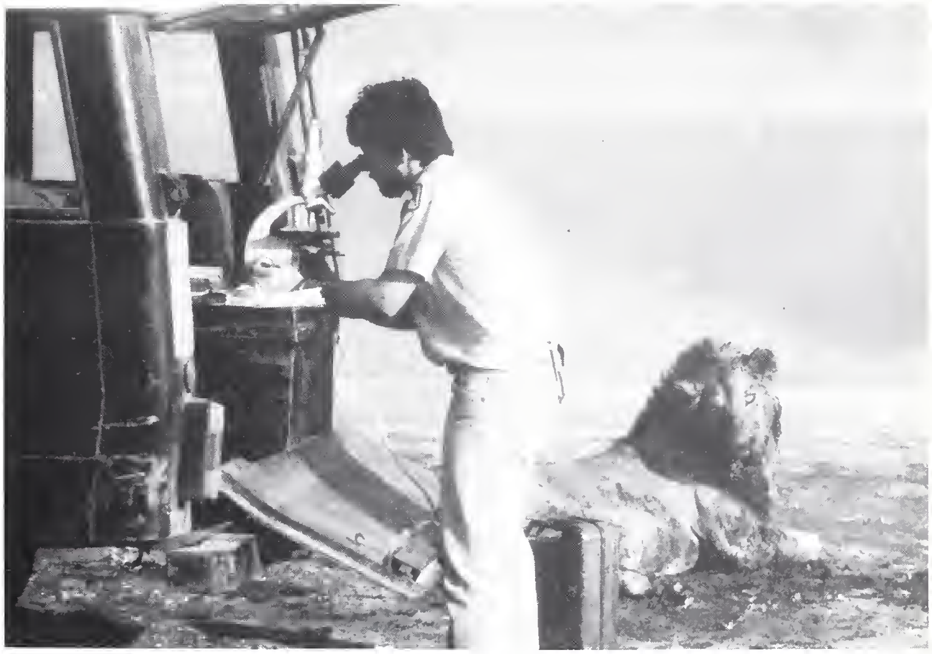
Wildt, who joined the NIH staff in 1980 and left in 1983 for the Zoo, continues to work out of the NIH Animal Center in Poolesville, MD, where he is adapting cryopreservation techniques to sperm and embryos of a wide range of species, including endangered cats, elephants, and koalas.

Already, Wildt's team has delivered the first in vitro (test tube) domestic kittens, all of which are alive and well. In early August 1989, his team delivered the first kitten conceived as a result of laparoscopic artificial insemination. These and other techniques—developed for humans and domestic livestock—now are being developed to help the Florida panther, cheetah, tiger, and other endangered species reproduce more successfully. Wildt and his colleagues also have developed artificial breeding techniques for the domestic ferret, a very important model for the future management of the highly endangered black-footed ferret.

Wildt, O'Brien, and other scientists at NOAHS Center will continue to collaborate with conservation biologists throughout the world in monitoring and maintaining the genetic diversity essential to the survival of endangered species. That way, Laurie Marker-Kraus says, future generations will not have to live in a world without cheetahs, Asian lions, tigers, panthers, koalas, black-footed ferrets, and pandas. ■

In 1987 the NOAHS team returned to the Serengeti for follow-up studies of the genetics and social structure of lions in an effort to learn how genetics and survivorship interact in a free-ranging species.

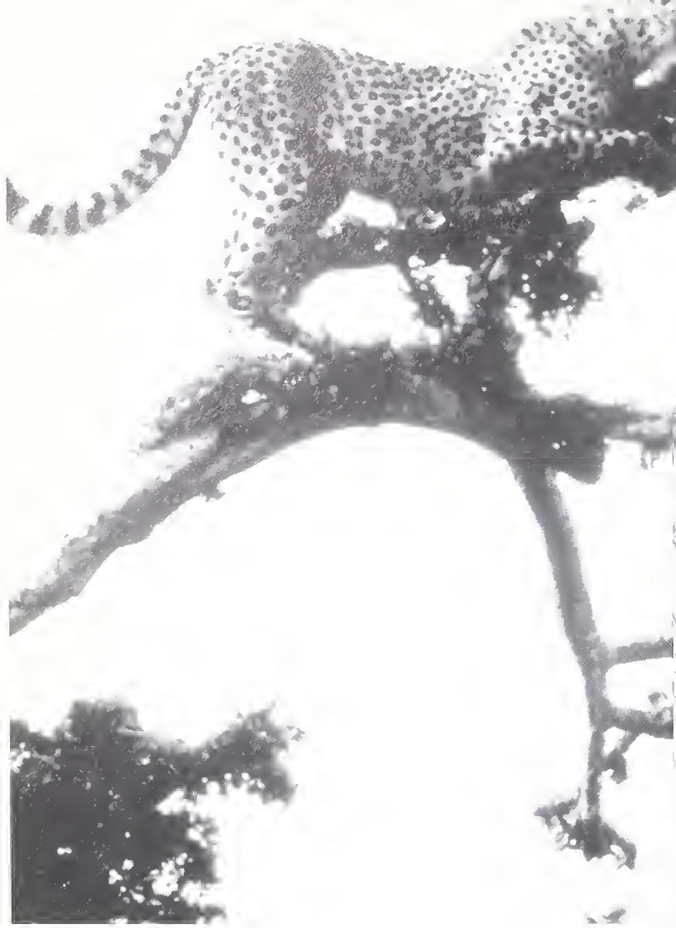
Dr. Mitchell Bush, Chief Veterinarian of the National Zoo, during a NOAHS team trip to the Serengeti in Tanzania, Africa. Behind Dr. Bush is "Noah," the team's traveling hospital and lab.



Fertility expert Dr. David Wildt of the National Zoo and NCI sneaks a quick look at a sperm sample as the African donor awakens.

Photos used in this story courtesy of Dr. Stephen O'Brien, NCI.

THE CHEETAH



"If we are to concede to the cheetah its place in the sun, we may yet save from extinction this creature so regal and aloof, so beautiful and lithe in movement, a symphony of natural grace."

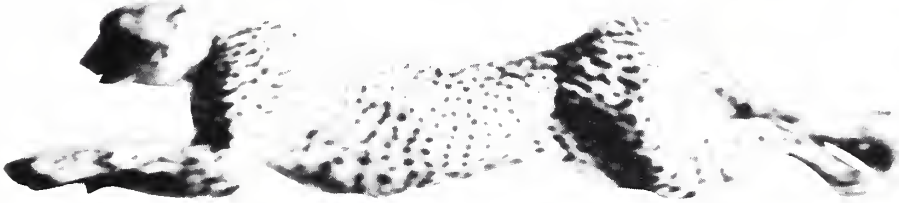
(Quote by Laurie Marker-Kraus, Director, NOAHS Center. Photo by Karl Ammann, professional photographer who lives in Nairobi and author of Cheetah.)

Laurie Marker-Kraus with the late Khayam, taken in 1986 in Oregon. Laurie raised Khayam from infancy and took the cheetah to Africa to teach her to hunt in the wild.

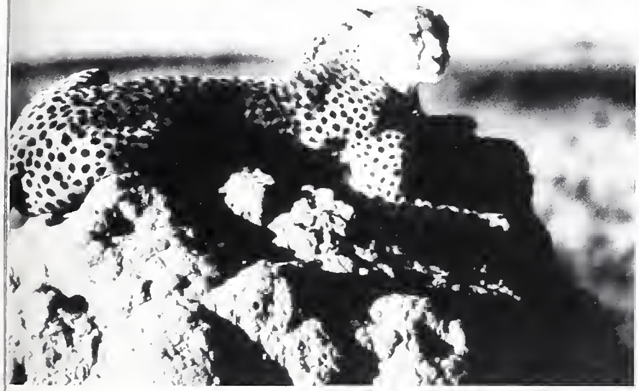
This painting depicts the cheetah in captivity. Kings and princes kept as many as 1,000 cheetahs as "hunting leopards" in the 14th, 15th, and 16th centuries. But the cheetahs in captivity never bred until 1956.

A three-month-old cheetah cub born at Wildlife Safari Park in Oregon. A cheetah lives 8 to 10 years in captivity, and probably as long in the wild. **(Photo by J. Golden of Winston, OR.)**

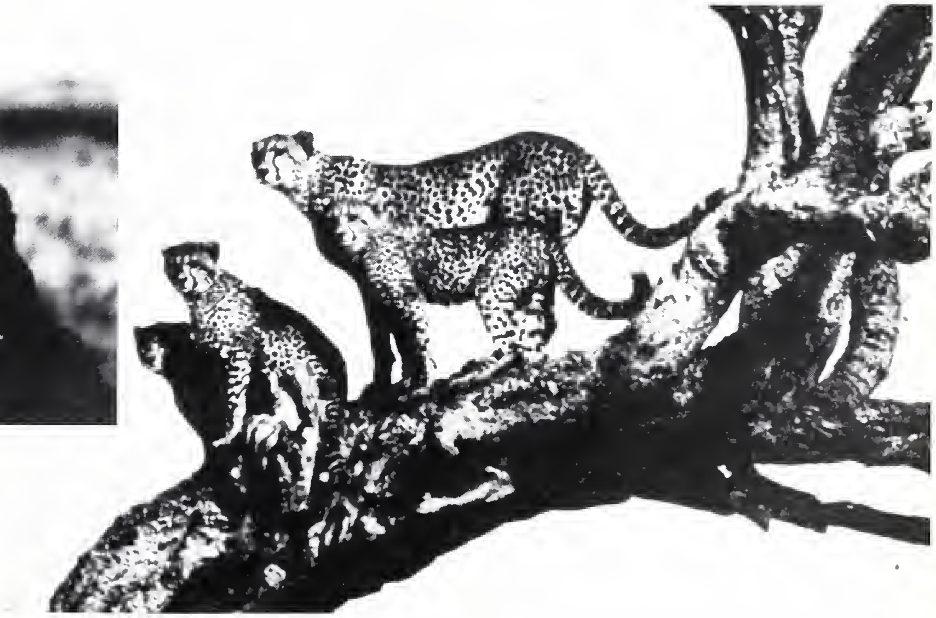
Cheetahs hiss to look ferocious, but basically are non-aggressive and believe in flight rather than fight. Cheetahs have trouble competing for food with other predators in protected reserves.



The cheetah is the world's fastest land animal. It can sprint about 70 mph for distances of about ¼ mile. **(Photo by Karl Ammann, professional photographer who lives in Nairobi and author of Cheetah, a photo essay.)**



Cheetah on rock outcropping, looking for its prey of steenbok, wildebeest, small antelope, mammals, and birds.



Cheetah mother with six-month old cubs in Kenya. She will stay with her cubs until they are 18 months old. **(Photo by Clayton Freiheit, Director of the Denver Zoo.)**

Cheetah photos courtesy of Dr. Stephen O'Brien, NCI and Laurie Marker-Kraus of NOAHS Center of the National Zoo.

Photo captions and special assistance from Maureen Mylander, NIH.

Layout and design by Mitzi Fuller.

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Miniature Poodles with RP Shed Light on Human Disease

Joyce Doherty

Retinitis pigmentosa (RP) is a set of inherited retinal degenerations that affect otherwise healthy teens and young adults. The RP types differ in time of onset, severity, and progression, but all have the same end stage—partial or total blindness. Currently, there is no cure or treatment for the 100,000 Americans who now have RP.

Research on these degenerations has been difficult because human donor tissue is scarce and is often obtained from RP patients with end-stage disease. Cell cultures of RP tissue cannot reveal information about disease progression. Now, National Eye Institute (NEI) scientists have discovered—using the dog model—that a fatty acid essential for the stability of a certain retinal cell is neither produced in the cell nor, because of an apparent metabolic error, supplied to the eye from an outside source.

Initially, RP affects the retinal photoreceptor cells, called rods and cones. The first photoreceptor cells affected are the rods, the cells responsible for night and side vision. Often, the first manifestation of RP is a progressive night blindness and tunnel vision. Next to deteriorate are the cones, which are responsible for fine, central vision and for color vision. Eventually more cells of the retina are affected and vision deteriorates to the point of either partial or total blindness, often before a person reaches the age 40.

One reason laboratory research on RP has been so challenging and progress so elusive is that RP can be inherited in three ways, each resulting in a different disease progression. A child can inherit RP through a faulty gene carried on the mother's sex-determining X-chromosome; through a faulty gene from one parent that dominates its normal counterpart from the other parent; or, through faulty genes from both parents who do not manifest the disease but can pass the gene to their offspring. Moreover, genetic variations within these basic inheritance patterns can also result from changes in the genes after conception.

Most genetic diseases involve some inborn error of metabolism. In these types of disease, no gross structural abnormality is present at the start, so scientists have been searching for some biochemical aberration that prompts the metabolic error leading to the disease process. As a result, biochemists have been investigating a number of retinal proteins, enzymes, and lipids for clues to a biochemical anomaly that leads to RP.

Certain miniature poodles naturally develop a rod-cone degeneration that follows the same pattern and has the same end-stage blindness as human RP. Blinding retinal diseases are not uncommon among highly in-bred dogs, like poodles. Because a dog ages faster than a human, scientists can see the disease progress over a few months, rather than years as with humans. Moreover, like humans, poodles have "daytime-adapted" sight, so the proportion of their rods and cones is similar to that of humans. Rodents, cats, and many other research animals with highly developed night vision have proportionately more rods than humans.

To investigate the traffic patterns of basic nutrients in the eyes of affected dogs, Dr. Paul O'Brien and his associates in the Cell Biology Section of the NEI Laboratory of Retinal Cell and Molecular Biology tagged several fatty acids with radioactive markers and injected them into the eyes of anesthetized dogs—some affected and some normal. Eye tissue samples were taken and by identifying the radioactive tags, the scientists could then follow what biochemical changes had occurred in the tissues and where.

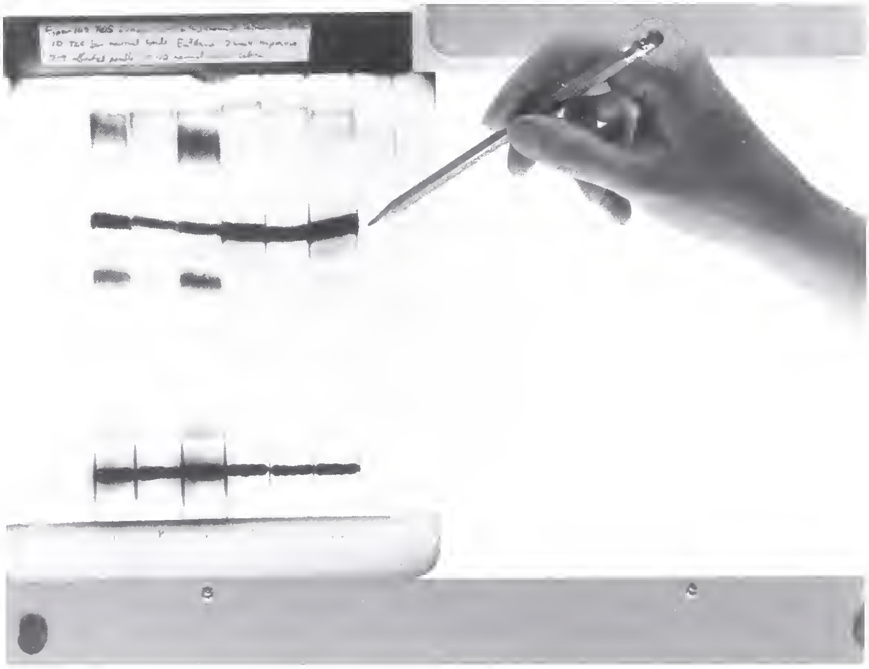
One retinal lipid that the scientists studied is the fatty acid, docosahexaenoic acid, or 22:6. Normally, levels of 22:6 are very high in the rod outer segments, suggesting that it is critical to some function of the rods. Rods require a rich supply of fatty acid nutrients to recharge the metabolic action needed to convert light energy into synaptic impulses and to replace the rod outer disc membranes that are shed regularly. In RP, the first observable deterioration occurs when sloughed-off disc membranes at the outer tip of the rod are replaced at slower-than-normal rates.

The precursor to 22:6 is a fatty acid called linolenic acid, or 18:3. The scientists found that, although the injected precursor became incorporated in the lipids of the rods, it did not convert to 22:6 as they had expected. This was true for both the affected and normal dogs. Because of this, the scientists deduced that the retinal tissue normally relies on some other organ, possibly the liver, for its supply of 22:6.

When the scientists measured 22:6 in the plasma of the dogs, however, they found that the levels were much lower in the affected dogs. If the affected dogs do not get adequate 22:6 from the circulating blood, the fatty acids normally damaged by oxidation would not be replenished. This, in turn, would lead to a depletion of a fatty acid essential to the replacement of rod outer segments.

Although more work must be done to confirm these findings and many questions remain about that is causing the apparent systemic defect, this dog model provided the first clue that the cause of a retinal degeneration lies outside of the retina. Moreover, this work provides some intriguing possibilities for treatment. Dietary supplement of 22:6 may be a way to compensate for the underlying biochemical defect and thus prevent disease development.

Scientists have also found abnormally low plasma levels of 22:6 in human RP patients who have the X-linked and dominant forms of the disease. If the affected dogs respond to dietary supplementation, the scientists believe that these RP patients may also benefit from similar therapy. ■



Radioactive bands on a thin layer chromotography plate identify the lipid containing 22:6, the major fatty acid in the rod disc membrane.

Animal Models Help Advance Basic Research

Doris Brody

To the naked eye they resemble flecks of lint. In the soil beneath your feet, hundreds of thousands of them live, multiply, and die undetected. They are tiny roundworms called nematodes, some of which are parasitic, but most of which are harmless. One species of nematode, *Caenorhabditis elegans*, is being grown in many different laboratories, where scientists observe closely as the creatures develop from egg to embryo to larva to mature worm. These studies are helping researchers, many of them supported by the National Institute of General Medical Sciences (NIGMS), unravel the complex set of events that lead a fertilized egg to form specialized cells at specific times during its development.

Such basic research, which is not targeted to a specific disorder, is crucial to understanding how living systems work in health and disease. Because there are so many disorders about which scientists know very little, an increased foundation of knowledge is essential to finding satisfactory treatment, and cures for human illnesses. Much of this basic research must be conducted in whole organisms rather than in single cells or parts of cells. Only within the complete system can the influence of various components on each other be studied.

In *C. elegans*, researchers have an excellent model in which to study cell growth and development, thanks to a massive project initiated more than 20 years ago in England. More is known about the development of *C. elegans* than about any other multicelled animal. Every cell division that occurs in the nematode's 3½-day life cycle has been traced. It is the first time the complete cell lineage of an organism this complex has been determined.

Now many researchers are studying such aspects of this nematode's development as interactions between cells, cell growth factors, and the specific effects of various genes. One group of NIGMS-supported researchers is studying mutations in a set of six "touch cells" that are the first step in a nerve-to-muscle cell circuit by which *C. elegans* responds to touch stimuli. These scientists have identified and characterized 18 genes that must act at various stages in the organism's development for the cells to differentiate into mature, functioning touch cells. The researchers have also discovered that touch cell differentiation can be modified by interactions with other cells. This work will enable scientists to study in detail the molecular mechanisms involved in touch cell differentiation.

Fruit Flies Aid Studies of Genetic Control

Since the genetic code was first "cracked" in the early 1960's, scientists have discovered many unexpected complexities in the way DNA and other components of the cell interact to sustain life. Just understanding how genes—stretches of DNA that generally code for specific proteins—are regulated (turned on and off) is extremely difficult. Recent NIGMS-supported studies of proteins encoded by genes that control embryonic development in the fruit fly *Drosophila melanogaster* provide an important step toward understanding gene regulation.

About 5 years ago, researchers began to locate specific genes, called homeotic genes, that control development in Drosophila by regulating groups of other genes. They know that these genes control aspects of development because of the basic foundation of knowledge about Drosophila genetics provided by nearly a century of research on developmental patterns in these flies. When the scientists sequenced—determined the order of subunits of—these genes and compared the sequences with other Drosophila sequences and with sequences from other animals, they found an area, called the homeobox, that was almost identical in creatures ranging from yeast to humans. Homeobox genes are believed to perform regulatory functions in all these organisms.

Nematodes (Caenorhabditis elegans), animals that aid studies of cell specialization, in the act of mating.

Photomicrograph courtesy of Anne Villeneuve and Barbara Meyer, Massachusetts Institute of Technology

Of course, biologists studying DNA regulation want to know exactly how the homeobox regulates gene expression. They have suspected that the homeobox genes in fruit flies control gene expression by coding for proteins that bind directly to specific DNA sequences. Now, NIGMS-supported researchers and their associates have conducted experiments that prove that gene expression is initiated by Drosophila homeobox proteins through direct binding to DNA. Moreover, these researchers have shown that different homeobox proteins can bind to the same stretch of DNA and that, in some cases, combinations of these proteins can increase or decrease the expression of a gene. This observation helps explain how regulatory genes provide control over early developmental events. The researchers suggest that the activity of the target gene depends on exactly what combination of homeobox proteins is bound.

So far, the experiments have been conducted only in cultured cells. The next step in understanding this type of genetic control in fruit flies will require studying the embryos themselves. Since there is some indication that certain homeobox genes may be involved in mammalian cancer, further understanding of the genetic control of development may have implications for understanding this disease.

Gene Therapy in Humans May Result from Studies in Mice

Scientists would like to be able to cure genetic diseases by correcting the defective DNA. However, because so little is known about what happens when genes are transferred, this must first be studied in complex, living organisms other than man. Naturally, the more that is known about the genetics of the model animal, the easier it is to study the transferred DNA and its effects on the rest of the system. Mice are the animals most often used in these studies, because it is relatively easy to work with them, much of their genetic makeup is known and the mouse has the necessary level of complexity to conduct this research. Moreover, there are many specifically bred strains of mice available to scientists.

Four years ago, the discovery of new vectors that could efficiently transfer pieces of DNA into cultured cells led researchers to hope that they would soon be able to begin experimental trials of gene therapy for selected human genetic diseases. Unfortunately, these trials have been delayed, in part because it was found, in studies involving mouse cells, that the transferred DNA did not always work as expected.

This four-winged mutant fruitfly (Drosophila melanogaster) helps scientists study genes that control embryo development.
Photo by E.B. Lewis, courtesy of Welcome Bender, Harvard University

For gene therapy to be successful, the gene must not only be taken up by the cell, but it must also be adequately expressed—that is, the cell must make the protein product specified by the DNA and make it in quantities sufficient to correct the defect involved in the genetic disease. So far, genes transferred into cultured cells and into animals have usually been expressed poorly, if at all.

Although this news is discouraging, especially for people with genetic diseases and their families, progress is being made toward understanding the mechanism of gene transfer. For instance, scientists are learning more about ways to target genes to specific sites within the cell's DNA. This is important because inserted DNA often integrates in a random fashion, but researchers think that if new DNA can be targeted to integrate into the site where it is normally found, it should be expressed better.

NIGMS grantees are at the forefront of research in gene targeting. They have shown that by using a mechanism called homologous recombination, they can target a correct DNA sequence to a specific defective gene in cultured mouse cells. Although the new DNA corrects the defective gene, the technique is a long way from the refinement necessary for human gene therapy. Homologous recombination may also benefit humans by enabling researchers to induce mutations within specific genes in mouse embryos, thus providing a tool with which to create mouse models for the study of many human genetic diseases.■

Animal Model Shows Susceptibility to Arthritis Linked to Brain's Regulation of Inflammation

Patricia Blessing

A research team from three different branches of biomedical science has provided—for the first time—biologic evidence of a defect in the brain's response to inflammation in an animal model of rheumatoid arthritis. Recent work published by this team in the *Proceedings of the National Academy of Sciences* (PNAS, April 1989) showed that differences in the body's response to stress play a major role in susceptibility and resistance to the development of arthritis in two inbred strains of rats; one strain is susceptible to arthritis, the other is not. In another issue of PNAS, the researchers report that the defect is in the brain's hypothalamus and its ability to produce and release a hormone critical in regulating the body's response to inflammation.

"Having found a defect at this site is consistent with the concept that the brain has a controlling effect on the development of arthritis," said Dr. Ronald L. Wilder, a rheumatologist at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) who has spent the last 10 years studying differences between the two strains of rats. "Having shown that regulation is being exerted at the level of the brain, we now have the means to understand this disease at a fundamental, molecular level."

The PNAS papers represent a collaboration among intramural scientists of the NIAMS, the National Institute of Mental Health (NIMH), and the National Institute of Child Health and Human Development (NICHD). Colleague Dr. Ester M. Sternberg, also a rheumatologist with the NIMH and NIAMS, was led by her interest in brain chemical messengers and diseases of inflammation like arthritis to collaborate with Wilder to explore brain mechanisms that may allow the disease to develop in one group of rats and not in another.

The two strains of rats are called Lewis and Fischer rats. Researchers can induce arthritis in Lewis rats by injecting a component of streptococcal bacteria (cell wall material); they cannot induce it in Fischer rats given the same component.

Yet, in a series of experiments Wilder and Sternberg observed inflammation, including arthritis, in the Fischer rats after treatment with a drug that blocks the effects of powerful anti-inflammatory hormones called corticosteroids. By blocking the action of corticosteroids in the Fischer rats, the researchers found that the animals were no longer protected, and the rats developed inflammatory arthritis. The researchers showed that the Lewis rats had a profound defect in the part of the brain that normally initiates the release of corticosteroids in response to stressful stimuli.

The brain is equipped with a circuitry system to counteract the effects of inflammation and to respond to other stresses. Both immune and central nervous system components are involved in the loop, now called the hypothalamic-pituitary-adrenal-immune axis, and it releases a cascade of hormones when called into action. For example, when cell wall material is injected into the Fischer rat model, immune system cells alert the brain's hypothalamus to produce corticotropin releasing hormone, or CRH. CRH, in turn, sends a signal to the brain's pituitary gland to send out another hormone, adrenocorticotropic hormone (ACTH). When ACTH reaches the bloodstream, it triggers the adrenal glands in the body to produce corticosteroids that suppress inflammation that is induced by the streptococcal well walls. This pathway also is a critical component in regulating the body's reaction to stress—increasing heart rate, blood pressure, and muscle tension.

Without a stressful event, the axis networks of both the Fischer and Lewis rat work similarly. But with an injection of bacterial cell walls, Fischer rats respond by increasing their production of CRH—and eventually of corticosteroids—thereby preventing joint inflammation. In the Lewis rats, on the other hand, the brain's circuitry does not respond, no additional hormones are released to curb the inflammation, and arthritis develops. By measuring the amount of different hormones released in this pathway in the two rat strains, the researchers showed that the Lewis rats' arthritis goes unchecked because they do not produce and secrete CRH in the hypothalamus.

Corticosteroids are the most potent anti-inflammatory agents in the body. The importance of corticosteroids in rheumatoid arthritis has been known for some time; a Nobel Prize was awarded in the 1950s for the demonstration of their powerful suppressive effect on inflammation in the joints of arthritis patients.

Over the years, arthritis research generally has focused on local factors at the site of inflammation in the joint, rather than on the possible role of other factors, such as brain mechanisms, in arthritis. "Traditionally, it has been very hard to get scientists to believe that there is a connection between the brain and a disease that appears in the joints," said Wilder. "There has been suspicion and suggestive evidence for nearly 40 years that the hypothalamic-pituitary-adrenal axis may be involved in arthritis, but it has been very hard to prove."

These studies provide the first evidence that inflammatory arthritis in an animal model results from an inadequate regulatory step that involves both the immune system and the brain. Sternberg and Wilder suspect that this mechanism may be relevant to other diseases as well because the Lewis rat is susceptible to a variety of other inflammatory and autoimmune diseases.

The investigators caution that a similar defect in this circuitry has yet to be proven in humans with the disease. The animal model, however, gives researchers a headstart as to where and how to look for these kinds of differences. They will continue their work at the molecular DNA level to explore the connection between the brain's responses to stress and susceptibility to arthritis.

The NIAMS and NICHD are components of the National Institutes of Health. The NIMH is a component of the Alcohol, Drug Abuse, and Mental Health Administration. ■

Dog Colony Provides Clues to Nacrolepsy's Secrets

Louise Williams

It's almost like a scary dream. A scientist tries to fit together the pieces of a puzzle. But every time he makes a connection, he sees another new puzzle, its pieces mingling with all the others.

A multiplicity of puzzles is what faces scientists investigating the sleep disorder, narcolepsy. And until recently, they had few ways of even sorting the pieces of one puzzle from those of another.

That nightmare may be over, however, thanks to a colony of narcoleptic dogs that is helping scientists unravel the mysteries of not only narcolepsy, but also of sleep itself.

The National Institute of Neurological Disorders and Stroke (NINDS) is the focal point within the Federal Government for research on narcolepsy and other disorders of the brain and central nervous system. The NINDS funds the unique dog colony—the only one in the world—which is part of Stanford University's Center for Narcolepsy and Related Disorders, located in Palo Alto, California. The Center studies the physiology, pharmacology, neurochemistry, immunology, and genetics of canine and human narcolepsy.

For the 250,000 Americans suffering from narcolepsy, the condition is unrelenting; the disorder envelops them in a perpetual fog of sleepiness, uneased by any amount of nighttime rest. Throughout the day, they experience mistimed attacks of dreaming, bouts of rapid eye movement (REM) sleep, normally restricted to nighttime slumbers. Narcoleptic REM sleep can be dangerous, striking at such inopportune moments as while driving a car.

Narcolepsy's other symptoms include cataplexy (a complete loss of muscle tone) and auditory hallucinations. Both symptoms also are mistimed elements of dream sleep, when the body becomes physically, but not mentally, inactive. At night, a REM period might take an hour to commence; in narcolepsy, a REM bout hits fast, the entire episode then lasting only minutes.

Through the years, studies of human narcoleptics have raised intriguing questions about what might be going awry, causing the brain to suddenly fall asleep. But until a chance encounter led to the discovery of the disorder in dogs, no guideposts existed to set investigators on the road to an answer.

Discovering A Clear Link

Scientists needed an animal model that would sift factors linked to the disorder from extraneous ones. They suspected a hereditary root for human narcolepsy, but could not tell how many genes might be at work.

Genes are the units of heredity and lie like beads on a thread to form chromosomes, which occur in 23 pairs. Genes instruct the body's manufacture of every organ and molecule, from eye color to quantities of hormones. Ideally, investigators wanted an animal affected by narcolepsy caused by a single gene.

This quest for such a clear link proved futile until a chance encounter in the 1970s brought the director of the Stanford Center, Dr. William C. Dement, before a group of veterinarians for a lecture on sleep disorders. One veterinarian present related having seen a poodle with narcoleptic-like symptoms.

Dr. Dement examined the animal and found it suffering from excessive daytime sleepiness and fits of cataplexy, usually provoked by the excitement of play or eating.

Dr. Dement brought the poodle to Stanford and quickly began contacting veterinary clinics throughout the country, trying to locate other narcoleptic dogs. He hoped to breed the animals for the disorder, thereby establishing a colony of dogs, all with clearly inherited narcolepsy.

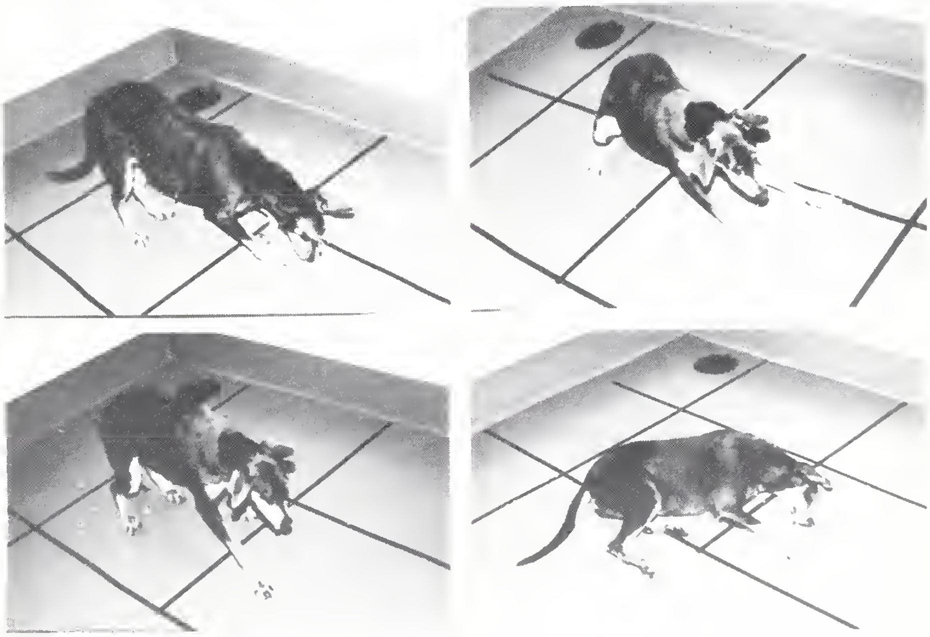
Excitement dimmed somewhat as early breeding attempts failed to produce the much sought-after model. More dogs were found, but their offspring did not show narcoleptic symptoms.

Even though they might carry a narcoleptic gene, "they were not clinically diseased," explains Dr. Emmanuel Mignot, a visiting assistant professor at Stanford and coordinator of the Center's basic sciences research.

Scientists tried mating other breeds and finally succeeded with Doberman pinschers and Labrador retrievers. "All the offspring of the Dobermans and Labradors, as well as of their mixed breeds, have narcolepsy, suggesting that the same gene is responsible," says Dr. Mignot. The disorder was definitely being transmitted by an autosomal recessive gene, he adds.

A gene is either dominant or recessive, depending on whether one or two copies of it on the alternate chromosomes produce a trait. Two copies of a recessive gene—on paired chromosomes—must exist for canine narcolepsy.

Offspring inherit one pair of chromosomes from each parent. Hence, the colony dogs have only the narcoleptic gene. The Center now houses about 70 dogs of those breeds and mixtures of the two.



A narcoleptic dog collapses to the ground with cataplexy (complete loss of muscle control).

Deciphering the Mysteries

Finding an animal model for narcolepsy already has opened many new doors for research. For example, Center scientists can better explore the disorder's natural history.

Humans first display symptoms between the ages of 10 and 30, with some narcoleptics eventually becoming severely disabled by age 40. Since symptoms do not appear for years, does the narcolepsy gene "turn on" at some time? Or is the gene always functioning, its effects only later becoming visible?

Among narcoleptic dogs, "the disorder develops when the young puppies are 100 days old, their puberty," says Dr. Mignot. "But we suspect abnormalities exist before then that can't be seen clinically. We're trying to detect those abnormalities."

While some narcoleptic sleep symptoms, such as hallucinations, cannot be identified in the dogs, many other REM characteristics are easily spotted. For instance, dogs twitch their muscles and bark during dreaming.

The lag in narcolepsy's onset may also result from an interplay between genetics and immunology. Immunological responses vary by individual, because everyone's genes determine their production of the types and amounts of chemicals used to identify and destroy foreign invaders. Could the narcoleptic gene prescribe a harmful immunological response?

Scientists now believe such genetic predisposition occurs, giving rise to "autoimmune" disorders, in which the body mistakes some of its own cells for invading substances. The body then begins destroying itself.

The body's front-line defense against invaders is lymphocytes or white cells. Lymphocytes spot an invader and produce antibodies, which help destroy the foreign substance.

Human narcolepsy is now thought to be associated with proteins lying on the surface of these white cells, notes Dr. Mignot. The proteins are called human leukocyte antigens (HLA).

Many types of HLA exist—genes determine which type the body manufactures. Each type responds differently to invaders, with certain ones apparently causing autoimmune reactions and, perhaps, narcolepsy.

Worldwide studies show virtually all human narcoleptics possess a certain HLA molecule, referred to as the DR2 marker. By contrast, only 25% of non-narcoleptics have DR2. This link between marker and disorder is the strongest yet discovered for any suspected autoimmune disorder.

However, as Dr. Mignot cautions, the link's rationale remains uncertain. "We do not know why it exists or even if narcolepsy is an autoimmune process. The DR2 marker may merely lie close to a gene," which causes narcolepsy. Or something still unknown may be responsible, he stresses.

The dog model allows Center scientists to trace DR2's descent in families, a chore nearly impossible among humans, since one, two, or even more genes may affect narcolepsy's inheritance.

As Dr. Mignot notes, "Canine narcolepsy's transmission lets us trace the disorder through the dogs' lineages and start looking for genetic markers that will lead us to the gene itself."

The Chemistry of Dreams

The Center also is seeking improved treatments for the disorder, necessary for several reasons. First, even through current drugs ease some symptoms, they lose effectiveness over time—and narcolepsy lasts a lifetime.

Furthermore, narcolepsy's two major symptoms—excessive daytime sleepiness and cataplexy—must be treated separately, often causing adverse drug interactions. For example, a drug against cataplexy may bring on the sleepiness another medication tries to counter.

Finally, currently prescribed drugs, mostly amphetamines and antidepressants, have adverse side effects, including dry mouth, palpitations, emotional changes, and impotence.

Center scientists are investigating a new type of drug, which would act on highly specific neurochemical reactions in the brain.

Brain cells communicate via chemicals call neurotransmitters, which are released by one nerve cell to attach like a key in a lock to specialized receptors on a nearby cell, altering its membrane's permeability.

Some drugs intensify a neurotransmitter's effects, but others may act more selectively, targeting a subset of the chemical's usual receptors.

Preliminary studies of the colony dogs indicate the presence of regional abnormalities in either neurotransmitters or their receptors. By radioactively labeling the neurotransmitters in dog and human tissue cultures, the scientists are gauging how well chemicals bind to specific receptors. Ultimately, a therapeutic drug may be possible that mimics neurotransmitter specificity.

Dreams of Normal Sleep

Not all treatments are years down the road, however. Studies with the colony may soon yield at least one new treatment.

Tests indicate that a drug called yohimbine, used for treating human impotence, reduces narcoleptic symptoms in dogs and has few adverse side effects. The drug is now undergoing human trials.

"There are species differences in drug responses," says Dr. Mignot," so we don't know yet if it will be as effective in humans as dogs."

Such new therapies may finally dispel the fog gripping narcoleptics' lives. But narcoleptics, human and animal, won't be the only beneficiaries of the newfound knowledge.

"Everyone experiences REM sleep," observes Dr. Mignot, "yet no one knows why. Although narcolepsy is not common, it also is not the only sleep disorder. People also suffer from secondary disorders of REM sleep, including depression.

"If we find out what's happening in narcolepsy, the repercussions would extend far beyond that disorder."■

Animal Models Important in AIDS Research

Sandy Hecker

Animal models are making important contributions to the study of the human immunodeficiency virus (HIV), the cause of AIDS, particularly in understanding the virus' effects on the body.

"Although unparalleled advances have taken place over the last eight years, much work needs to be done to understand how an individual infected with HIV can remain clinically well for extended periods before symptoms appear," said Anthony S. Fauci, M.D., NIAID director and NIH associate director for AIDS research. "The development of additional drugs with low toxicity and high therapeutic benefit, as well as vaccines, is needed. Because AIDS is a fatal disease that presently has no cure, animal models for the testing of potential therapeutic agents and vaccines are essential to ensure continued progress in our efforts to control this disease."

The human immunodeficiency virus (HIV), the cause of AIDS, infects only humans and chimpanzees naturally, and chimpanzees have not yet developed fatal HIV-related disease. Small, easy-to-manage research animals such as mice or rabbits that contain HIV or related viruses are providing valuable information to scientists. Development of appropriate animal models is critical because harmful viral effects in a living person may be compounded by complex ongoing processes—such as metabolism or an active immune response—that cannot be duplicated by computer models or in cell cultures.

Mice

A promising mouse model was developed by members of the NIAID Laboratory of Molecular Microbiology (LMM). Former LMM medical staff fellow John M. Leonard, M.D., LMM chief Malcolm A. Martin, M.D., and their colleagues produced mice with complete copies of HIV genetic material in every cell of their bodies. Because they contain genetic material from another organism—HIV—in addition to their own, the mice are called transgenic. "Obtaining information about how HIV induces disease in infected people and ultimately destroys the immune system is a high priority of AIDS research. This can't be learned from the tissue culture systems currently available," said Martin.

Seven (called "founders") of the 64 first generation mice contained complete copies of HIV DNA integrated into their chromosomes and later transmitted the copies to their transgenic offspring. None of the founder mice showed any signs of disease, but about one-half of the offspring of one founder developed symptoms that were apparent 10 to 12 days after birth. The affected animals weighed 50 to 60 percent less than their unaffected littermates. The researchers found that some of the affected mice spontaneously developed disease with many of the features of AIDS.

Preliminary work by Martin and his colleagues has shown that HIV in the mouse cells can be induced to express viral proteins. These results indicate that the mice could be a useful model for testing therapeutics to prevent HIV-induced disease. The transgenic mice are also expected to help researchers better understand HIV effects in the body.

Chief Herbert C. Morse, III, M.D., and his colleagues in the NIAID Laboratory of Immunopathology (LIP) have developed an AIDS-related mouse model. These mice are infected with a unique set of retroviruses (LP-BM5 MuLV), which result in physiological abnormalities in the mice that are similar to those seen in humans infected with HIV. The researchers are using their mice to study the detailed response of the immune system to viral infection, while others are using the mice for early stages of testing potential AIDS therapies.

LIP senior scientist Sisir Chattopadhyay, Ph.D., LIP section head Janet Hartley, Ph.D., and Morse have shown that although LP–BM5 can induce disease in the mice, the LP–BM5 viral mixture is missing components that are required for viral replication, thus a "helper" virus is necessary for spread of the infection to other cells. Studies of the products of LP–BM5 are expected to promote understanding of how retroviral proteins can alter immune system cell function and have pathogenic effects.

Morse and his colleagues have found that the primary immune system cell targeted by the viruses in their model is the macrophage, which is a major target for HIV in humans. Together with Laboratory of Viral Diseases visiting fellow Ambros Hugin, M.D., they are deciphering the interaction of B and T cells—the critically important immune system cells—during infection.

Morse and his colleagues have found that the dysfunctional T cells in retroviral infections are related to the presence of abnormal B cells. If abnormal T cells are eliminated, mouse B cells are not abnormal. The group has also shown that if abnormal B cells are eliminated, T cells are not abnormal. These results demonstrate the complex interactions between subsets of these immune system cells that the researchers are working to understand. Elucidation of the initial step in the pathway leading to abnormal B and T cells in their model could provide key information applicable to understanding human infection with HIV and its concomitant pathogenesis or disease-causing effects.

Rabbits

An important model for the study of HIV infection and AIDS is the rabbit model developed by former NIAID Laboratory of Immunogenetics (LIG) senior staff fellow Henrietta Kulaga, Ph.D., LIG chief Thomas J. Kindt, Ph.D, and their colleagues. The researchers successfully infected rabbits with HIV by injecting them with HIV-infected human T cells.

Kulaga and her colleagues confirmed that the rabbits were infected by observing that their blood could transmit HIV infection to susceptible human cells, and by using diagnostic tests such as the western blot, which detects antibodies made against HIV. Within 6 weeks of injection, the rabbits developed antibodies against HIV. A technique called polymerase chain reaction (PCR) was used to confirm the presence of HIV genetic material in two types of cells—in T cells circulating in the blood, and in spleen cells—that would be expected to harbor the virus. PCR is a newly developed technique that enables researchers to detect smaller amounts of specific DNA sequences than was possible with older techniques.

All infected rabbits were periodically examined for illness, swellings, lesions, and for evidence of neurologic disorders. Examination of the infected rabbits after death revealed enlarged spleens, and pathologic tests indicated immune cell infiltration of the lungs and spleen. These conditions are typically seen in humans with AIDS.

By radioactively labeling the HIV-containing cells injected into the rabbits, the researchers showed that, after 2 hours, these cells were no longer circulating in the rabbit blood. Tracing indicated they were in the rabbit kidney and other places that collect cellular debris prior to degradation and disposal. In a second experiment, PCR studies showed that HIV took 6 weeks or more to infect the rabbit T cells and spleen cells. Taken together, these two findings indicate that there is active replication of HIV in Kindt's rabbit model.

The research team has identified parameters of infection necessary for standardized use of the rabbits in AIDS vaccine and drug development. A patent has been filed covering these procedures. A private company, RRI, Inc., based in Vienna, VA, has received a license from NIH through the National Technical Information Service (NTIS) to use the procedures to test potential vaccines and drugs on a commercial scale at its research facility in Frederick, MD. This license is the first to be granted for an animal model from NIH.

Kindt and his colleagues are also using their rabbit model to study precisely what is happening in HIV infection—where HIV goes in the body, details of the infectious process, whether the rabbit immune system is compromised, and how this can be measured.

Larger Models—Cats and Monkeys

Important questions about the interaction between the AIDS virus, HIV, and the immune system have been difficult to answer because ideal animal versions of AIDS have not yet been developed. Georgetown University molecular virologists Philip Johnson, M.D., Vanessa Hirsch, D.V.M., D.Sc., Robert Olmsted, Ph.D., under contract with the NIAID Laboratory of Infectious Diseases (LID), and LID section head Robert Purcell, M.D., and their colleagues are developing feline (cat) and simian (monkey) models of infection with HIV-related viruses.

The researchers are studying the pathogenic effects of the feline immunodeficiency virus (FIV), first isolated in 1986. In April 1989, Johnson and his colleagues were the first to publish an article on the molecular cloning of FIV—that is, the procedure by which researchers determine the precise message in FIV's genetic information.

Johnson and his colleagues are also studying the simian immunodeficiency virus (SIV), in macaque monkeys. FIV and SIV are members of the lentivirus family to which HIV also belongs. The LID-affiliated researchers are interested in how genetic variation among individual FIV and SIV isolates affects disease progression in their hosts. This information has important implications for development of HIV therapies and vaccines to prevent infection.

Monkeys

Vaccine researchers, hit hard by the lack of an animal model, have turned to monkeys infected with SIV, for clues to designing a vaccine to prevent AIDS.

Both HIV and SIV gain entry into immune cells through a docking site called the CD4 receptor, located on the surface of T lymphocytes. When rhesus monkeys becomes infected with SIV, the animals' immune systems eventually become weakened in ways similar to those of people with AIDS. In these monkeys, SIV infection causes immune system abnormalities that include loss of T4 lymphocytes, swollen glands, and production of antibodies against SIV.

Rhesus monkeys infected with SIV also develop diarrhea, loss of body weight, and brain abnormalities strikingly similar to those physicians see in humans. In addition, the monkeys develop the same opportunistic infections—pneumocystis pneumonia, yeast and cytomegalovirus infections—that occur commonly in people with AIDS.

SIV was first isolated from captive rhesus monkeys, an animal native to Asia, where no wild monkeys have been found to carry the virus. Although later studies showed that SIV is commonly found in certain wild species of African monkeys, the virus does not appear to produce disease in African monkeys. Scientists believe rhesus monkeys became infected with SIV while caged with healthy African monkeys that carried the virus.

SIV shares from 40–50 percent of its genetic makeup with HIV, with the genes of both viruses arranged similarly in the virus genome. This genetic kinship will provide researchers with insights into how the virus interacts with the immune system and how the body might be bolstered to protect against infection with the AIDS virus.

The goal of AIDS vaccine researchers is to develop molecules that confer upon the body an immunity to infection by HIV. These scientists try to mimic in people who have never been exposed to the virus the lifelong immunity that often follows infection by a virus.

But development of an AIDS vaccine has been hampered by a lack of knowledge about whether the immune system ever develops resistance to HIV. Scientists hope to solve this problem by studying in detail the response of the monkey immune system to SIV infection. Tracking the progression of the disease will help scientists identify key immune reactions that may play a role in immunity to HIV.

Vaccine researchers will identify and tease out SIV molecules that stimulate the body's immune defenses and determine whether these defenses prevent the virus from establishing an infection. With this basic information in hand, researchers can then construct prototype vaccines from these components and test them for their ability to block SIV infection in monkeys. Because of the similarity between HIV and SIV, researchers hope to replace SIV molecules with corresponding ones from HIV for use in candidate vaccines in humans.

Scientists will also look to this animal model to study the virus' troublesome ability to mutate rapidly and to learn what effect this has on the immune system's ability to fight the virus. This information will help them design an AIDS vaccine to protect against a range of HIV strains.

Because of the urgency of the AIDS pandemic, vaccine studies using SIV-infected rhesus monkeys are proceeding alongside parallel studies in humans. The SIV model is expected to give researchers much-needed tools to quickly address questions that cannot be asked in humans about the safety, effectiveness, and mode of action of candidate AIDS vaccines.

"Animal models are absolutely necessary for AIDS research because of the overwhelmingly lethal nature of the disease," said Fauci. Ethics and human compassion dictate that animal models be employed. The search for the ideal animal model continues, however enormous progress has already been made. As a result of a concerted scientific effort, animal models will greatly facilitate the testing of drugs and vaccines to combat this deadly epidemic."■

Animals Serve Fundamental Role in Preserving the Environment

Tom Hawkins

In a sense, it was animals that supplied the early warning on the environment that led to the establishment of the National Institute of Environmental Health Sciences. Indeed, it was the loss of birds and other wildlife in the food chain that alerted scientist and author Rachel Carson and impelled her to undertake the study that became the 1962 national best seller *Silent Spring*. As she recounted the ravaging of the food chain by synthetic chemicals in the pages of the *New Yorker*, and when the series was published as a book by Houghton-Mifflin, she soon ran into a wall of objections and denials. Unfortunately, as the Congress and public soon came to realize, the substance of her observations proved substantially correct.

Less than four years later, in 1966, Congressional mandate established what was called the Division of Environmental Health Sciences within the National Institutes of Health, and what then became, in 1969, the National Institute of Environmental Health Sciences (NIEHS), in Research Triangle Park, NC. NIEHS' mission is basic biomedical research on the human health effects of environmental agents. Because of the close interdependence of the human and non-human species, partly through the food chain, but inevitably through shared dependence of air, water and soil, what affects human health nearly always affects the larger community of species.

The NIEHS' challenge has always been immensely difficult scientifically—to single out one or sometimes two or three interactive contaminants in the environment among thousands of such agents, and to single out these contaminants even when the human exposure is at very low doses and over very long periods of time, and to determine which contaminants cause diseases. And that is only the beginning of the assignment. The NIEHS must then discover exactly how the offending agent enters the body, is stored, is transported, and how it finally comes to act within the body to cause disease. Scientists spend years in quest of the precise cellular and molecular mechanisms by which the damage is done, and then after many years of additional research begin to devise methods through which environmental disease can be prevented and treated.

Importance of Animals in Scientific Process

Animals are interwoven in the process of scientific discovery every step of the way. They serve as one of several basic tools together with epidemiology, tissue and microbe cultures, computer experiment design and data analysis, and other sophisticated technologies, useful in answering questions about the exquisitely intricate processes of life. Laboratory animals, principally rats and mice, are vital to scientific research, but all animal species—wildlife, companion animals, farm animals—are beneficiaries of an environment made safer for life.

Human health has been a continual beneficiary of animal studies. Indeed, seven compounds have been identified as human carcinogens only after they were found carcinogenic in animal studies. These are 4-aminobiphenyl, diethylstilbestrol, mustard gas, vinyl chloride, aflatoxin, bis(chloromethyl)ether, and melphalan. Animal studies of diethylstilbestrol done at NIEHS indicated the drug's ability to cause cancer in the female offspring of mothers treated with DES, as well as DES' ability to cause reproductive malformations in male as well as female offspring of treated mothers. These effects were later confirmed in human patients as well. These findings gain even greater significance when it is recognized that a number of environmental contaminants are estrogenically active and may behave similarly to DES.

Animal studies at the NIEHS-funded center at University of Rochester indicated the toxicity of methylmercury, which affects hearing, eyes, kidney function, and the nervous system, as well as causing birth defects. The animal studies enabled investigators to relate human health effects to methylmercury exposures. Other studies have shown the bioaccumulation of methylmercury in large saltwater fish such as tuna and swordfish, and more recent studies have detected similar accumulations in freshwater fish taken from inland lakes, alerting public health officials to a significant potential source of human methylmercury exposure.

Air Pollution Studies

Air pollution research has depended heavily on animal studies to determine which health effects to study in humans. Longterm, NIEHS-funded air pollution studies at Harvard University used animal data to determine the toxicity endpoints in collecting human data comparing health effects of air pollution in six different U.S. cities. Later, the study was expanded to offer similar comparisons among 24 different cities. A senior NIEHS scientist explains, "Without the animal work, researchers wouldn't know what to look for in humans." And he also points out, "Animal work will guide us toward better organ function tests. The ones we use now clinically are amazing primitive."

Animal research also has been a key to recognizing the toxic effects of ozone—not the protective layer high above the earth, but the "bad" ozone trapped near the ground. Animal studies of 18 years ago are now the key to studying human health effects of both ozone and carbon monoxide.

Often it is mixtures of contaminants that cause human health effects. Animal studies pointed up the danger of mixtures of ozone, acid, and small particles. Working from animal data, scientists have been able to clarify the human effects. We now know that some minor effects of lung function once thought reversible are not, and that these dangerous mixtures of pollutants have a direct effect on increasing emphysema and asthma.

Similar progress has been made in determining the toxicity of synthetic industrial chemicals such as PCB's, where animal studies showed the chemical's capacity to cause birth defects, liver changes, and effects on behavior and learning. The animal studies pointed to the higher levels of PCB's in mother's milk and led to human studies of accidentally exposed people in Taiwan and the People's Republic of China. The effects of PCB's on skin pigmentation and its depression of the immune system were also first understood through animal studies.

NIEHS-funded studies at New York University of bis(chloroethyl)ether and bis(chloromethyl)ether in rats and hamsters led to studies in occupationally exposed humans that quickly established these compounds' carcinogenicity and led to their abandonment as chemical intermediates in industry. This animal research undoubtedly prevented much human disease and death.

Research Using Non-Mammals

In addition to research using mammals, the Institute has long been a lead agency in the study of aquatic species. Aquatic species in some studies serve as sentinels to detect pollutants in the wild, and scientists also use them as laboratory animals or study them as a vector of human exposure through seafood, as in the case of methylmercury mentioned earlier. A surprising variety of aquatic species are studied—horseshoe crab, flounder, blue channel crab, and trout are only a few examples.

In the fall of 1988, NIEHS hosted a major international conference on chemically contaminated aquatic food resources and human cancer risk. Conference presentations pointed up the complexity of assessing the risk presented by carcinogens in seafood, the multiple variables including mixtures of, and quantities of carcinogens, variable seafood/fish consumption rates, interaction with carcinogens from other sources, and variable cooking procedures, among others. Some of those attending also expressed concern about potential human reproductive and neurotoxic effects of contaminants in seafood.

Tumors in trout on a fish farm led researchers to trace the tumors to the grain the fish were being fed, and in turn this led to the identification of the naturally occurring aflatoxins in the grain as powerful carcinogens. Further, the synergism between viruses and aflatoxin were first observed in animals. NIEHS-funded research is currently seeking to identify the metabolites of aflatoxin active in this synergism.

In order to explore the scientific usefulness of "lower" animal forms, NIEHS is investigating the feasibility of using earthworms in the lab, as a possible way to study the metabolism of contaminants. The "fruit fly" Drosophila has long been a superb species for studying genetics and the effects of chemical contaminants on genes.

The responsible and humane use of a variety of animals in the laboratory has made possible better scientific information and more effective health policy and regulations in handling scores of environmental contaminants and other compounds. These include asbestos, (DES (diethylstilbestrol), BCME (bis(chloromethyl)ether, vinyl chloride, AAF (2-acetylaminofluorene), aflatoxin, and heavy metals including lead, cadmium, and mercury. Without such scientific knowledge, careless use and inadvertent exposures to these contaminants could cause cancer, reproductive defects, neurological disease, and other chronic health problems in the human population and in other species as well.■

Healthy Older Animals Offer Clues to Healthy Human Aging

Karen McCrory Pocinki

Healthy older animals play a vital role in aging research. Major progress in establishing the causes, natural history, treatment, and prevention of a number of age-associated diseases has come about largely as a result of studies with laboratory animals. This type of research continues to provide valuable information that will improve both human and animal health.

The similarities in aging processes between some animals and humans makes animal studies, particularly studies of rats and mice, a most valuable source of scientific information. By controlling an animal's genetic composition through careful breeding and ensuring healthful diet and safe environment, scientists can derive meaningful scientific data from animal investigations that could not be obtained easily from studies in humans.

Early in the 1970s, many investigators involved in research on aging agreed that it was difficult to obtain animal models to carry out their studies. In order to conduct valid and reproducible research on the processes of aging, scientists need aged experimental animals possessing well-defined and uniform characteristics reared under strictly controlled conditions. Recognizing that many investigators did not have the facilities or the resources to develop and maintain colonies of healthy older rodents for research, the National Institute on Aging (NIA) established a number of such colonies and currently makes these animals available to NIA-supported scientists.

Large colonies of rats and mice are bred and raised to healthy old age. Four types of rats and 10 types of mice are housed in an environment that is free of specific bacterial and viral agents, maintained at a comfortable 70 degrees Farenheit (plus or minus 2 degrees), and fed a nutritious diet. Animals range in age from 3 to 36 months. All of the animals are monitored regularly for genetic purity and any evidence of disease. The objective for maintaining these colonies is to provide *healthy* animals for aging research.

The original rodents were obtained germfree by caesarean section and subsequent generations are kept free from common rodent bacteria and viruses. As the animals age, important scientific data are collected relating to their patterns of growth, their development of any age-associated diseases, and their life span. By providing this valuable resource, the NIA hopes to aid scientists in their attempts to understand the mechanisms of aging. The welfare of the animals is of prime importance for ethical reasons and because the outcome of these studies depends in great part on the health of the research animals.

A number of NIA-supported research projects rely on carefully bred rodents. The ultimate goal of basic research in aging is to learn enough about aging processes and age-associated diseases to be able to intervene effectively so that older people can live healthier lives longer. The NIA currently supports projects with laboratory animals aimed at developing such meaningful interventions.

For example, researchers have found that animals fed unrestricted diets are not as healthy and do not live as long as animals that are not overfed. This nutritionally optimum diet is achieved by restricting the caloric intake of the animals to substantially less (20 to 60 percent less) than that of the animals fed unrestricted diets. To date, caloric reduction is the only intervention that has been shown consistently to be effective in extending life span.

Feeding animals nutritionally optimal diets greatly extends their maximum life span and decreases the incidence of cancer and other diseases common in later life. Restricting energy intake without causing a deficiency in essential nutrients appears to retard the rate of aging in almost all species tested so far. Nearly all studies have involved rats or mice and all studies continue to indicate that calories are the critical nutrient that must be restricted in order for aging and diseases to be affected.

Researchers believe that caloric restriction increases the life span of rodents by retarding aging processes. Age-associated changes, many of which appear to be related to deterioration, can be delayed or prevented by food restriction. Examples include a delay in the decline of the immune system with age, the prevention of decline in the older mouse's ability to learn a complex maze, and a delay in age-related reproductive changes in female rats.

In addition, caloric restriction has been found to delay the occurrence of most age-associated diseases or to slow their progression. For example, scientists recently found that when female mice were fed reduced calories starting at 24 days of age or at 61 weeks of age, they had strikingly fewer tumors than animals that were not restricted. In a related study, feeding mice a reduced calorie diet inhibited the development of leukemia. Researchers also have found that kidney disease in rats is forestalled by dietary restriction. The results of these studies appear to be due to a reduction of calories rather than to the elimination of a specific nutrient or toxic contaminant in the diet.

These and other findings are beginning to provide scientists with a better understanding of the beneficial effects of caloric restriction on aging processes. Future research will focus on exactly how caloric restriction works to retard aging and age-associated diseases, on whether dietary restriction can slow aging and prevent disease in primates in a fashion similar to its effects in rodents, and on whether all of this information will translate into recommendations that can be made to improve the health of human populations.

Progress in aging research depends on the continued use of laboratory animals to further knowledge of growth, development, and aging processes. The valuable scientific information gained from the study of these animals is vitally needed to prevent disease and improve the nation's health.■

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Special Issue: Healthy Living, Healthy Aging

Photo, Bill Branson, NIH

"I can't give you a recipe to live long—life is how you live, how you sleep, how you eat, how you drink, how you work—life is what you are."

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About the cover: Healthy Living, Healthy Aging

Dora Zins, 103 years old

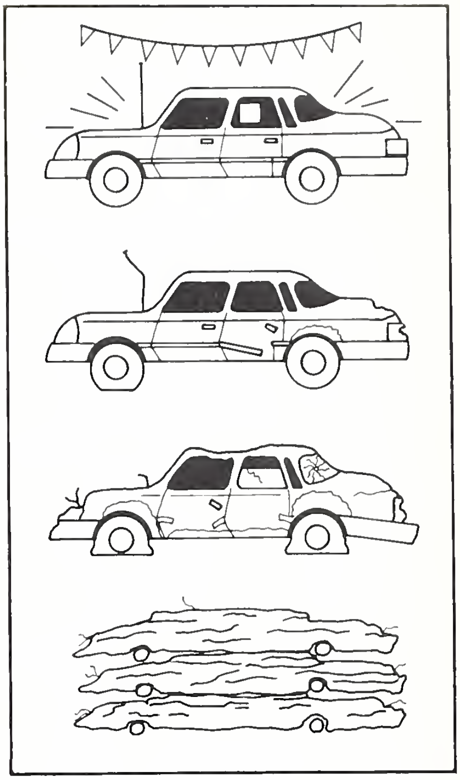
This issue of *News and Features* is dedicated to the theme "Healthy Living, Healthy Aging." While there are many people who continue to view old age as synonymous with illness and dependence, modern research has found that nothing could be farther from the truth.

To know with no degree of uncertainty that people can live to very late years as vital and functioning members of society is like a breath of fresh air. Older people do not automatically suffer heart disease, lose their mental faculties, or enter nursing homes. That is not the way life has to—or should—end.

There are proven ways to eliminate, or at least modify, illness in later life. Good nutrition, a sensible exercise program, regular physical examinations, moderate, if any, use of alcohol, and cessation of smoking all contribute to a healthier prognosis. Scientists tell us that there are benefits which can be realized from improving one's lifestyle at any age. It is never too late to adopt health promotion and disease prevention strategies.

On the cover of this magazine is a photograph of healthy, alert Mrs. Zins. She is 103 years old. We have no accurate count of how many people in the United States have passed their 100th birthday. A conservative estimate is 25,000. The question which intrigues scientists is what can be learned from these people to enable more of us to reach our 100th birthday in good health and mental function. The challenge is great, the potential staggering.

T. Franklin Williams, M.D.
Director
National Institute on Aging



Wear and Tear Theory

Why do some people age faster than others? The question is a perplexing one and one that has researchers from a variety of research disciplines seeking answers. Theories range from a purely genetic orientation to one based upon environmental assaults. See page **2**

Researchers—supported by the National Institute on Aging (NIA)—have found that grandparenting is in vogue. Three, four and even five generation families are experiencing family relationships nearly unheard of just a few decades ago. There often comes a time, however, when many older people must depend on others for assistance. Researchers are teaching families to adjust to their new role as caregiver and to develop creative methods to meet the needs of all family members. See page **10**

Various Theories Attempt to Solve the Puzzle of Aging

Pamela W. Jones

Immortality and the possibility of renewing youth have captured the imagination of mankind from before the time of recorded history. Five thousand years ago, the Babylonians told the epic story of the king and hero Gilgamesh, who sought, found, and eventually lost the secret of eternal life. The ancient Greeks and Romans ascribed immortality to their gods and the few humans who became gods. Magical potions to fend off death have been sought by cultures as diverse as the Chinese, the ancient Hebrews, and the Europeans of the Middle Ages.

Despite mankind's intense interest in longevity, scientists do not yet agree on precisely why or how humans age. In 1986, the National Institute on Aging (NIA), the Mount Sinai Medical Center, the American Museum of Natural History, and the Brookdale Foundation cosponsored a symposium on the "Modern Biological Theories of Aging." The purpose of the symposium was to examine several of the leading theories of aging and to evaluate the relevance of these theories to current and future research on aging. The proceedings of this symposium are scheduled for publication in late 1987.

Theories of aging range from the concept of purely genetic control of aging to the concept of environmental assaults to the organism, culminating in death. (Fig. 1) Most experts now believe that aging, which is extremely complex and variable, is not explainable by a single mechanism, but represents many phenomena working in concert.

Do We Age by Design or Error?

Most theories of aging can be divided into two general types: error theories and programming theories. (Fig. 2) Error theories are based on the premise that random events, for example environmental assaults, cause damage to the body's cells. This damage accumulates over time, resulting in cellular, molecular, and organ malfunction. Programming theories are based on the assumption that aging is programmed into the cell itself and, much like prenatal development and adolescence, is the expected result of a purposeful sequence of events written into the genes.

Wear and Tear

One of the oldest theories of aging is the wear and tear theory (Fig. 3), which states that humans, like automobiles, have vital parts that run down, leading to aging and death. At the molecular level, DNA is continuously damaged and the body has evolved mechanisms to recognize and repair this damage. (Fig. 4) A key question is whether the continuous DNA damage that occurs with aging is totally repaired or whether it accumulates, leading to molecular and finally organ malfunction. Many have studied these questions of DNA damage and repair, but there is as yet no clear evidence for an accumulation of such damage or for a decline in repair abilities with aging.

Theories of Aging

Figure 1

Theory	Proponent
■ Wear and Tear Theory*	Pearl (1924)
■ Rate of Living Theory*	Pearl (1928)
■ Metabolic Theory*	
■ Programmed Senescence Theory	Hayflick (1961)
■ Free Radical Theory	Harman (1955)
■ Error Catastrophe Theory	Orgel (1963)
■ Somatic Mutation Theory	Sziliard (1959)
■ Immunological Theory	Walford (1969)
■ Endocrine Theory	Korenchevsky (1947)
■ Collagen Theory**	Vertzar (1957)
■ Cross-Linked Theory**	Bjorlstein (1968)

* May Represent the Same Theory

** May Represent the Same Theory

NIH PHOTO 2158

Live Fast, Die Fast?

The so-called rate of living, or metabolic, theory argues that the faster an organism lives, the quicker it dies. The strongest evidence for this theory is the effect of calorie restriction on lifespan in rodents. In 1935, scientists at Cornell University severely restricted the caloric intake of recently weaned rats. The animals lived extraordinarily long lives. This finding was largely ignored until the 1960s, when new studies confirmed the early findings. Some studies showed that, even when older mice were given a restricted diet, lifespan was extended about 30 percent.

To date, calorie restriction appears to be the only intervention repeatedly shown to alter the rate of aging in animals. Although the exact mechanism by which calorie restriction causes increased survival is not known, we do know some of the physiological responses to calorie restriction. There are changes in the response to certain hormones controlling metabolism and in the composition of blood lipids (fats), as well as delays in certain age-related declines in the immune system.

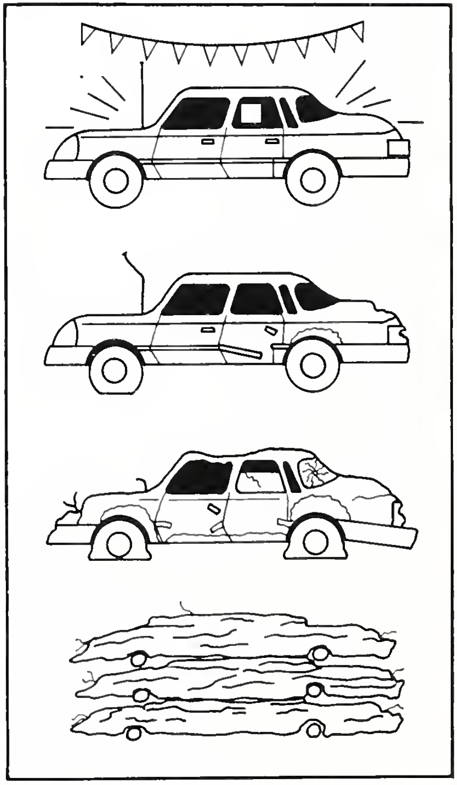
No conclusions can be drawn about the effects of calorie restriction in humans because no systematic study of undernutrition (reduction of calories, but an adequate intake of nutrients) has been carried out as yet in man.

Cross-Linking

Some have speculated that aging results from an accumulation of cross-links in proteins. Cross-linking occurs when small molecules with at least two chemically active sites attach to two protein molecules, or when active groups on separate protein molecules interact with each other. One particularly abundant protein in our tissues is collagen, the matrix material that supports cells and tissues. With aging, more and more cross-links form between collagen molecules. As a result, the collagen becomes less pliable. Although this process can explain a number of age-related changes, such as a reduced ability of the skin to stretch and flex, it is unlikely that this is a major contributor to aging.

Wear and Tear Theory

Figure 3



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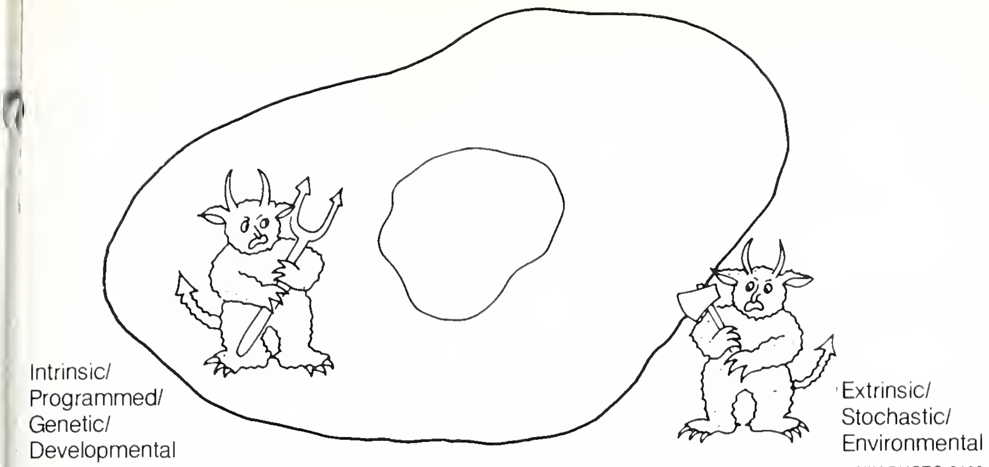


Figure 2

NIH PHOTO 2160

Free Radicals

The free-radical theory of aging focuses on the damaging effects of free radicals, highly unstable chemical fragments produced during normal metabolism that readily react with and often damage other molecules. Although free radicals are usually cleared from the body without causing functional damage, an age-related accumulation of free-radical damage may interfere with the vital work of key cell structures.

The body has evolved efficient ways of detoxifying free radicals, for example vitamins C and E are very effective free-radical scavengers (called antioxidants), capable of inhibiting free-radical reactions. In early experiments to measure the effect of antioxidants on free-radical damage, rodents were given vitamin E and survival was measured. The first experiments showed increased survival for animals fed vitamin E.

Analysis of these results revealed that the animals given large doses of vitamin E also had significant weight loss. Because we know that reduction of caloric intake and weight loss can increase survival in animals, a question remains as to whether the increased survival noted in these studies was a result of antioxidant action or a result of caloric restriction.

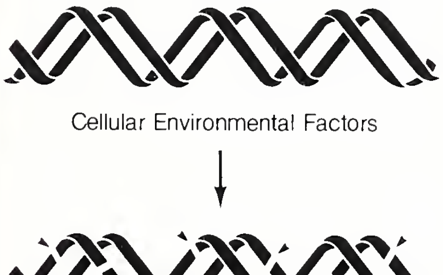


Figure 4

NIH PHOTO 2161

Although the free-radical theory was first proposed over 30 years ago, it has not yet been tested rigorously. Feeding antioxidants to animals and measuring their lifespans might not detect anything if free radicals are not the limiting factor in survival. We need to measure free-radical damage in various important cells as they age.

Error Catastrophe Theory

The error catastrophe theory, originally proposed in 1963, states that when damage to the protein-making machinery of the body occurs, faulty proteins will be synthesized and will gradually accumulate. This process of accumulating faulty proteins leads to "catastrophes," such as damaged cells, tissues, and organs.

This has proved to be a relatively easy theory to test, and a vast body of evidence now indicates that most protein modifications that occur with aging are probably due to changes in the shape of the protein occurring at some point after synthesis, not to the accumulation of errors during synthesis.

Although the error catastrophe theory does not appear to be valid, some investigators question whether currently available methods are capable of detecting the degree of damage that would be needed to alter cellular functions.

Programmed Senescence

This theory, one of the oldest, states that aging and death are programmed events, a result of the sequential switching on and off of certain genes. How would genes controlling aging manifest themselves? Some may act as biological clocks—for example, "programmed clocks" in humans bring on menarche and menopause, events that occur at specific ages with only minimal variation. There is also a clock for the involution (shrinkage) of the thymus, which plays a key role in the aging of the immune system.

How can we investigate the mechanisms of biological clocks? One model is the human cell cultivated outside the body. It was once believed that all cells cultured outside the body were immortal and could be stimulated to divide forever. But in the 1960s, scientists made the revolutionary discovery that normal human cells stop dividing after approximately 50 divisions. Although it is a vast oversimplification to say that we age and die because our cells stop multiplying, the discovery of a limited lifespan for normal cells provided a valuable impetus for research in many related areas.

If aging is programmed, what are the pacemaker organ systems? The endocrine (hormone) system and the immune system are two likely candidates.

Do Hormones Control Aging?

Some investigators have postulated that events occurring in the hypothalamus and pituitary are responsible for some important human aging processes. The pituitary, located on the base of the brain, secretes hormones that in turn stimulate other glands to produce hormones. Scientists have shown that by removing the pituitaries from animals and giving them injections of some of the essential hormones produced by the pituitary the animals' aging is slowed. Kidney damage was reduced, the rate of cross-linking was lower, and the immune system functioned better. It is also true, however, that animals without pituitaries weighed considerably less than control animals, and weight loss alone could produce all of the beneficial effects noted in animals undergoing pituitary excision.

Some believe that a biological clock in the hypothalamus (a region of the brain) instructs the pituitary to secrete a hormone that interferes with the ability of body tissues to respond to thyroid hormones . This theoretical hormone, referred to by some as the "death hormone," has never been isolated.

The Role of the Immune System

The immune system defends the body against bacteria, viruses, and other invading organisms. The thymus gland, located in the chest, is an essential component of the immune system. It reaches maximum size during adolescence and declines to the point where it is barely visible at age 50. There are parallel changes in a variety of immune functions, including an increasing failure to react appropriately to foreign agents or organisms ("non-self") and a tendency to react against the body's own tissues ("self"). This inappropriate immune reaction to "self" is presumed to be the cause of so-called autoimmune diseases, such as rheumatoid arthritis, in which the body produces antibodies to its own cells.

Proponents of the immune system theory assert that the programmed decline in immune system function leads, at least in part, to aging and death. By reducing the body's ability to fight infection, fend off cancer, and even repair

DNA damage, a decline in the immune system may be the single most important event in the aging process.

Birth of the Life-Extension "Industry"

Coinciding with efforts to find answers about the biology of aging has been an exploding interest among the public in physical fitness and nutrition. This growing public interest in health has helped create a life-extension "industry" whose leaders encourage the public to buy products touted to "enhance the human lifespan potential." Although some of the evidence supporting the claims of those promoting life-extension products is derived from valid scientific findings, it is far too soon to recommend complex dietary regimens (some of which include prescription drugs), drastic caloric restriction, or other unproven interventions as a means of prolonging life. What *is* accepted by most scientists is that lifestyle habits such as smoking cessation, moderate exercise, and balanced nutrition can certainly improve the quality of life and may prolong life as well.

Most experts now believe that aging, an extremely complex and variable developmental phase, is probably comprised of many processes operating at many levels of organization—molecules, cells, organs. Therefore, several theories may be needed to explain all aging phenomena.

The study of aging theories is an energetically growing discipline, and the search for mechanisms of aging is vitally important. Until we understand these mechanisms, it will be difficult to understand fully the nature of the diseases and disorders commonly associated with old age. Although it will take time to assemble the puzzle of aging, we have made much progress in identifying the first pieces. ■

Rate of Speech Found to Influence Comprehension for Many Older People

Barbara Katzman

"SLOW DOWN, I CAN'T HEAR YOU!"

This seemingly nonsensical statement has more meaning than first meets the ear.

Most people have a very clear—if incorrect—mental picture of an old person. All too often it is an image of a person who is sick or helpless, who has trouble seeing, hearing and getting around. Many of these negative stereotypes have been proven untrue but one which lingers is that older people cannot hear unless spoken to in a shout. The fact that 7 million people over the age of 65 in the United States do have a hearing impairment tends to reinforce this image. In fact, however, the speed at which a message is delivered rather than its volume may cause problems in comprehension.

Presbycusis, literally "old hearing," is caused by a combination of biological and environmental factors. It has been estimated that advanced presbycusis is apparent in about 13 percent of the population over the age of 65. The most common characteristic of this condition is lost sensitivity in the ability to distinguish between small changes in pitch, particularly at high frequencies. However, many older people with perfectly good hearing may still have difficulty following a movie or play. The question then becomes, "Why does this occur?"

Cognitive aging—age-related changes and stabilities in mental processes involved in the acquisition, organization, and application of knowledge—is of great interest to researchers. Of particular interest are "auditory processing deficits" experienced by people who hear well but who have difficulty comprehending what they hear. There are those who believe that this problem is a result of disease or medication or is a form of mental deterioration which is part of the normal aging process. New evidence suggests another explanation, as well as something that can be done about it.

At Brandeis University in Waltham, Massachusetts, NIA-supported scientist Dr. Arthur Wingfield and his colleagues are studying the theory that it is the speaker, rather than the listener, who often causes a problem in communicating. Most people speak at a rate of approximately 140 words per minute (wpm). Newscasters and performers may speak 200 wpm. Wingfield finds that though most older people have little difficulty at these speeds, increasing the speed further begins to present problems in recall and comprehension.

Wingfield's studies have shown that as people age their ability to comprehend the spoken word is vulnerable primarily for two reasons: information is imparted too fast and the incoming message is often disorganized. Wingfield found that as the rate of speech increases, an older person's ability to comprehend decreases. Furthermore, faulty grammar and complex sentence structure make it even more difficult to understand and recall a spoken message. Wingfield is pursuing the hypothesis that when the rate of speech slows many older persons can comprehend as well as younger ones.

In one of his studies, Dr. Wingfield divided participants into two groups. The first group varied in age from 18 to 22 years, the second from 65 to 73 years. All had normal hearing and all could demonstrate perfect understanding of several 5-word to 8-word combinations spoken at a normal rate. Both groups were composed of healthy people who had achieved at least a high school education and tested average or above in verbal ability.

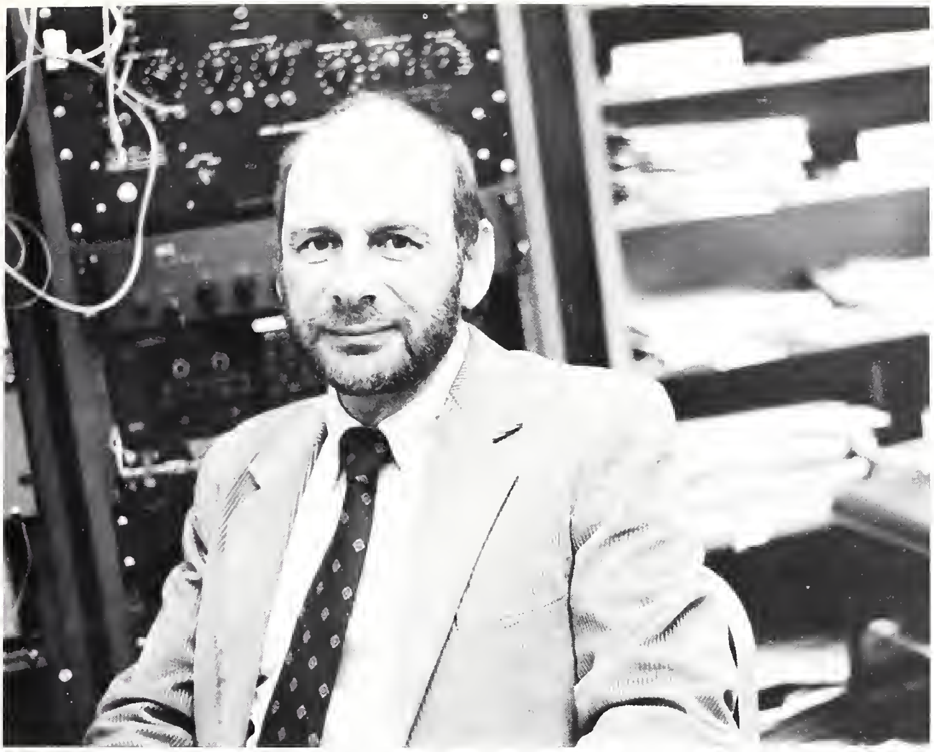
Each person was asked to listen to three sets of words: normal English sentences, grammatically structured sets of words which were devoid of meaning (syntactic strings) such as "colorless green ideas sleep furiously," and lastly a set of words totally devoid of meaning, or random strings. Each grouping was said at various speeds. Immediately after each word grouping participants were asked to repeat as accurately as possible what they had heard.

Results of the study clearly showed that older people are at a distinct disadvantage as the rate of speech increases. In fact, the older adults showed a decline in comprehension of rapid speech at an average of five times greater than the decline in younger adults' comprehension. However, follow-up studies found that effective use of grammar and clear organization of material compensated in large part for this decline and virtually restored comprehension to the level of the younger group. Additionally, older adults were found to depend upon the use of contextual information to a greater degree than their younger counterparts. (See Figure 1)

Further studies found that older people have a hard time understanding unnecessarily complex sentences and that they often simplify complex sentences in their minds to aid comprehension. This does not mean, however, that one must speak to an older person as one would to a child. There is nothing in Dr. Wingfield's study to suggest that such an approach would benefit older people.

There are some long-range implications to this study. Dr. Wingfield believes that, "although older persons may have far greater difficulty in comprehending rapid speech than do the young, this disadvantage can be overcome to a high degree by efficient use of linguistic context and general language knowledge. Speech communications will be most effective when it is viewed as an active partnership between speaker and listener."

When an older person says *"SLOW DOWN, I CAN'T HEAR YOU"* it very often is the truth, as Arthur Wingfield's study proves. ■



Dr. Arthur Wingfield is the recipient of the National Institute on Aging's (NIA) Merit Award. The primary purpose of this award is to provide long-term stable support to investigators whose research competence and productivity are distinctly superior.

Selection criteria for Merit Awards include: at least two previous grants totaling not less than 7 years of support, research consistent with NIA priorities, emphasis on the field of aging on previous and current research, and an investigator recognized as a leader in his/her field.

Photo courtesy of Dr. Wingfield, Brandeis University. NIH PHOTO 2162

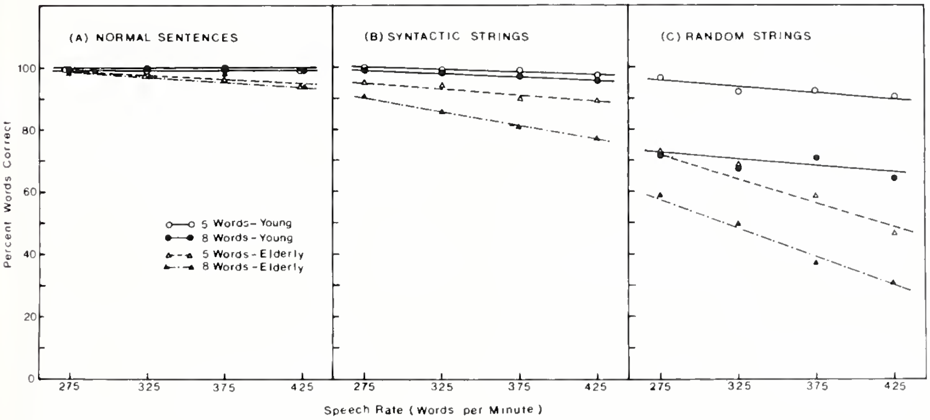


Figure 1.(A) normal sentences, such as "The green grass is wet," (B) syntactic strings (word sequences devoid of meaning but which follow grammatical rules, such as "colorless green ideas sleep furiously"), and (C) random strings (words which are both meaningless and devoid of grammatical structure, such as "sleep grass down low too"). NIH PHOTO 2163

Research Shows that Transdermal (Skin) Patch May Be an Improved Method of Administering Hormones

Virginia Morgan

A study at the University of California at Los Angeles showed that estrogen (estradiol) given by skin patch did not carry the risks of estrogens taken in pill form (conjugated estrogens). Yet, the patch appeared to be as effective as pills in maintaining calcium balance. NIA-supported scientists Drs. John K. Lu and Howard L. Judd measured the blood levels of estrogen in 23 postmenopausal women who received supplemental estrogens either orally or by skin patches. They also studied the effects of the two methods of administration on several liver functions.

The new method of administering estrogen through a transdermal (or skin) patch uses a transparent adhesive patch which is attached to the abdomen. Low doses of estrogen are absorbed from the drug reservoir in the patch. Each patch is used for 3 days. Because release of estrogen from the skin patch more closely resembles the way estrogen is released naturally by the ovaries—entering the blood stream without going first to the liver—scientists believe it may be a safer way to administer estrogen to postmenopausal women. Both methods raised the level of estrogen in the blood to similar levels. However, oral administration had significant undesirable effects on several liver functions, while transdermal administration did not.

At the time of menopause a woman's body markedly decreases its production of estrogen. One result of this decrease is an accelerated loss of bone (osteoporosis), especially during the several years immediately after menopause. Pills containing synthetic estrogen sometimes are prescribed for postmenopausal women to prevent or slow down the development of osteoporosis, a disease resulting in weakened bones that are prone to fractures. Currently, estrogen therapy is considered one of the most effective methods for reducing bone loss.

Persons at highest risk of developing osteoporosis include white (Caucasian) women who have early or surgical menopause (before age 45). Other high-risk factors include extreme inactivity, use of corticosteroid medicines (prescribed to reduce inflammation, especially in patients with arthritis), and having a slight build. A chronically low intake of calcium in the diet, smoking cigarettes, and an excessive use of alcohol also can contribute to the development of osteoporosis. When estrogen replacement is used to prevent bone loss, it usually is started soon after menopause and continues for the following 5 to 10 years.

The standard method of administering estrogen—through pills taken by mouth—has a number of adverse side effects, including an increased risk of developing gallstones and hypertension, which are caused by the effects of estrogen on the liver. In addition, patients often do not receive the full benefit of estrogens administered orally, either because the liver breaks the hormones down and removes them from the blood before they are fully distributed to the site of the action, or because the hormones are digested before they can act.

Skin patch administration of estrogen has several unique features that make it attractive. It delivers estrogen at a constant rate, resulting in sustained estrogen levels in the blood and constant rates of excretion; this allows the physician to monitor the circulating levels and easily adjust dosage. Also, the patch can be applied and removed without difficulty, which encourages patient compliance.

Although further studies are needed to confirm the safety of estrogen administration through skin patches, as well as its effectiveness in retarding bone loss, this research points the way toward an improved and safer means of replacing estrogen and preventing osteoporosis. ■

Menopause Poses No Problems for a Majority of Women Says NIA Study

Barbara Katzman

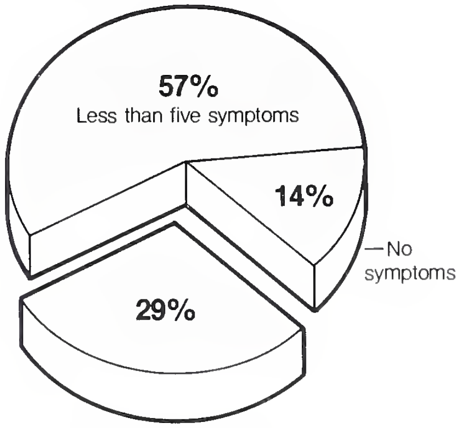
The term "change of life" conjures up visions of women confronted by menopause suddenly demonstrating Jekyll/Hyde personalities, as though menopause is an event that will dramatically alter the course of their remaining years. Common misconceptions of menopause range from losing one's sexuality, to developing profound depression, to depending upon drugs to cure problems and mitigate symptoms. Many people still view the menopausal woman as one beset by a host of physical, social, and psychological problems. Until recently very little research had been conducted to address these common myths and taboos.

Natural menopause occurs when menstruation ceases and the female body no longer produces an egg, or ovum, from which a baby may develop. In most cases menopause is a gradual process (called climacteric) lasting as long as 10 years. The process is considered complete one year after the last menstrual period. In some cases, due to surgery or radiation or chemotherapy treatments, premature, or artificial menopause occurs. To what extent, if any, women entering natural menopause experience symptoms similar to women who have undergone artificial menopause is a question that has never been fully addressed.

To respond to the need for reliable information, NIA-supported scientist Dr. Sonja McKinlay and colleagues at the American Institutes for Research in Cambridge, Massachusetts, have completed one of the first longitudinal studies of healthy women as they approach and experience menopause. The major goal of the study was to record factors that determine how a woman's physical and mental health are actually affected by menopause. The study enables a systematic documentation of changes that occur in women in terms of their attitudes and symptoms, as well as whether there is an increase in drug use, medical care, and social supports.

The knowledge from such a study bears special significance in a society in which an increasing number of women contribute to the work force, and estrogens and other potent medication often are prescribed during and after menopause. Additionally, with the life expectancy for women in the United States approximately 78 years of age, and menopause generally occurring between the ages of 50 and 52, women today can expect to live one-third of their lives beyond menopause.

How Many Symptoms Do Women Report in a Two Week Period



Five or more symptoms

The symptoms most frequently reported (by about 35% of women) were: lack of energy, feeling blue, headache, aches or stiffness in the joints and hot flashes. The least common, reported by 10% of women or less, were: dizzy spells, frequent cough, cold sweats, sore throat, loss of appetite and menstrual problems.

NIH PHOTO 2164

The initial stage of Dr. McKinlay's study included the development of a reliable definition of healthy menopause; a cursory look at the effects of estrogen therapy; a brief study on the effects of work force participation on the menopause; and an investigation into the effectiveness of social supports at a time when adult children often leave home, death or illness of older kin is common, and a reemphasis on work force participation often takes place.

Dr. McKinlay studied approximately 2,500 healthy women between the ages of 45 and 55, with no record of premature menopause caused by hysterectomy, radiation, or chemotherapy treatments. Each of the participants responded to an initial survey and was subsequently interviewed at regular 5-year intervals over a period of 10 years.

Results of the study disproved many common notions of menopause and supplied researchers with more detailed data than ever before collected. Some of the significant findings are as follows:

*The median age of natural menopause among women in the United States is 51.4 years. Smokers experience menopause an average of 1.5 to 2 years earlier than non-smokers.

*Natural menopause produces very little change in a woman's lifestyle. Aside from some bothersome symptoms, such as mild and occasional hot flashes and menstrual irregularity, postmenopausal women do not suffer from physical disabilities.

*Of the 75 percent of women who experience natural menopause, few report severe symptoms; they rarely depend upon medication for relief of symptoms, make infrequent trips to a physician for menopausal symptoms, and have lower incidences of breast surgery for benign conditions than women who experience surgical menopause.

*Stress and/or depression contributes to an increase in self-reported hot flashes.

*Employment outside the home seems to have a positive effect on health.

*Depression is not a significant factor for those who experience natural menopause. When depression was identified, it was associated with events and situations of mid-life and was largely unrelated to menopause.

*Women who have undergone surgical menopause (hysterectomy) seek the support of friends and relatives more often than women who have experienced natural menopause.

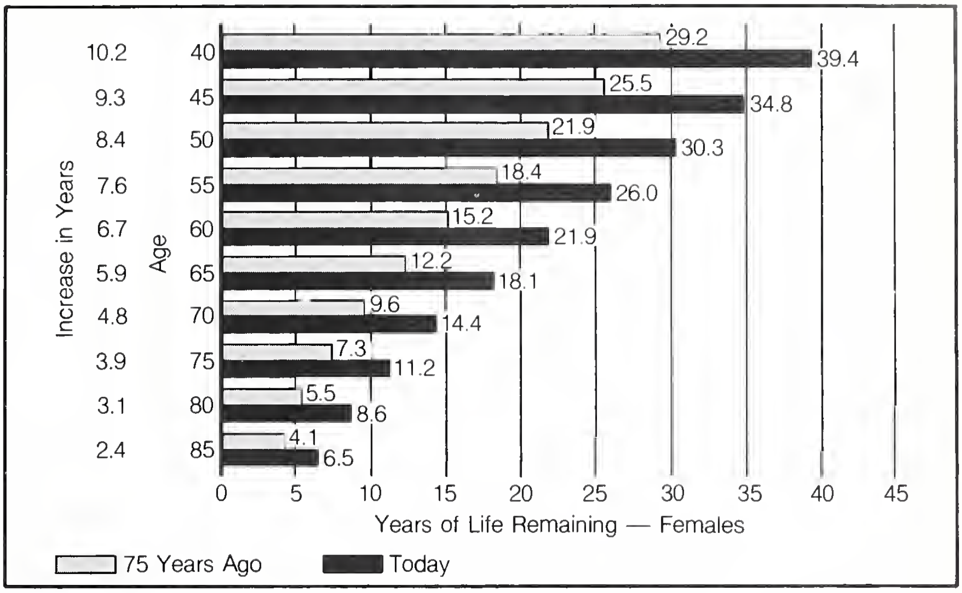
*Surgical menopause and radiation or chemotherapy treatment are associated with less education and poorer health or with higher use of medical services for other reasons. At this point in Dr. McKinlay's study no explanations for these associations were made.

*A clear majority of women—75 percent—express either relief or no particular feelings toward having arrived at menopause.

This study is an important breakthrough in understanding and accepting that menopause causes little or no disruption in lifestyle for most women. Dr. McKinlay hopes that her findings will provide, for the first time, a reliable picture of the normal range of experiences for women as they pass through menopause. According to Dr. McKinlay, "This normal profile will be invaluable for the clinician who sees only a small atypical subgroup in his/her office, as well as for women themselves, who right now have no clear idea of how normal their own experiences are."

Follow-up study will include further investigation on variables such as employment, education, social supports, and the use of oral contraceptives. Additional studies will include research into hormone levels as they affect menopause; the relationship between menopause and osteoporosis; and psychological profiles of women as they progress from pre- to post-menopause. The ultimate goal is to fully understand this normal biological event. ■

Life Span of Americans—How it has Lengthened



NIH PHOTO 2165

Is this the Dawning of the Age of Centenarians?

It may surprise you to know that centenarians—people who reach their 100th birthday—are the most rapidly growing age group in the United States. In 1985, there were some 25,000 centenarians, a 66 percent increase over 1980. Furthermore, the Bureau of the Census projects that there will be as many as 50,000 centenarians in 1990 and 100,000 in the year 2000, thus doubling and tripling the present population.

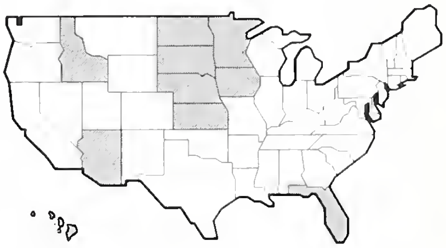
Centenarians are a curiosity to both the public and scientific community. Everyone wants to know just what it is they do or do not do that enables them to live so long. The fact is, the chances of becoming a centenarian are very slight—about 1,150 persons in 100,000, according to 1979-81 Census Bureau data. It appears that women are more likely than men to reach the century mark, and, also, that geography plays some part. For example, your chances of reaching 100 are more favorable in Hawaii than in the District of Columbia.

The longest living American is thought to have been Mrs. Fannie Thomas, who died in 1981 at the age of 114. The oldest person in the world was probably Shigechiyo Izumi of Japan who died last year at the age of at least 120.

In conjunction with the National Institutes of Health (NIH) Centennial celebration, the National Institute on Aging (NIA) designated July 1, 1987 as Centenarians Day. It seems very appropriate, if not overdue, that a day be set aside in honor of this exemplary and remarkable group of people. A number of centenarian-related activities were planned. They included a ceremony for local centenarians in Washington, D.C. as well as in the governors' offices around the country, radio and television shows about centenarians, newspaper coverage, health fairs, displays of century-old artifacts in libraries and museums, radio programs featuring music popular in the 1880's, and intergenerational exchanges, such as children recording oral histories of elderly people within their communities. ■

JoAnn Pass

Ten States With the Most Favorable Chances of Surviving from Birth to Age 100
United States, 1979-81

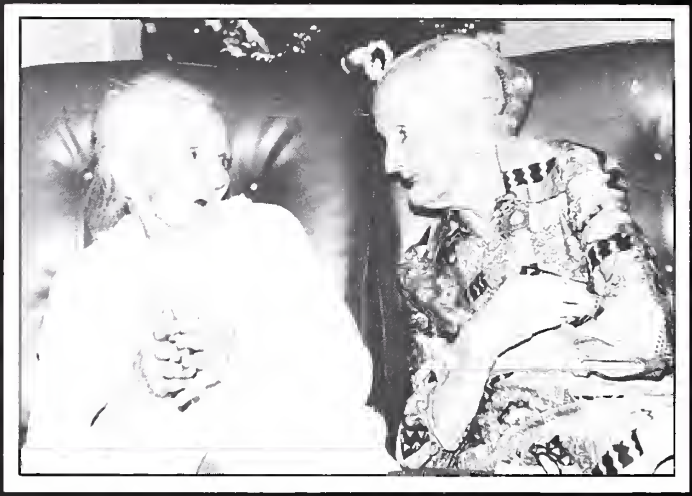


State	Chances per 100,000
Hawaii	1713
Minnesota	1444
South Dakota	1392
Iowa	1379
Nebraska	1364
North Dakota	1362
Kansas	1339
Florida	1336
Idaho	1329
Arizona	1317

National Center for Health Statistics

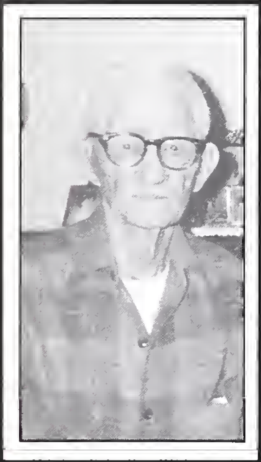
NIH PHOTO 2166

Deborah Balthaser
Born: June 7, 1885
Hometown is Leesport, Pennsylvania.
"I owe my long life to eating the right things."
Photo, Bill Branson, NIH



Maggie Grubb Lambeth (left) and Allie Grubb Hill
103 year old twins.
Denton, North Carolina.
Photo courtesy of Suzi Ciupitu, The Denton Record

Carl Erastas Nielsen
Born: February 13, 188
Native of Scipio, Utah.
Other than aspirin,
never used any
medication until this yea



M.G. Moses Turner
Born: January 26, 1886.
Resides in Drumright,
Oklahoma.

Dr. Robert Leslie
102 years old.
Brooklyn, New York.
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Jane Stovall
Age: 102
Resides in Sarasota,
Florida.
Enjoys doing her own
cooking.
"I hope to wear out an
not rust out."

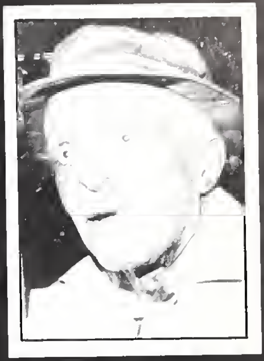
Clara Pauli
Born: February 19, 1887
Hometown: Kearney,
Nebraska.
Now resides in Winner,
South Dakota.
Photo courtesy of Dan Bechtold

Clara Myles
Born: December 11, 1886
Native of Woodville, Mississippi.
Her secret to a long life: "Just live!"
Photo courtesy of Ray Spruell

Marie LeCompte-Hotar
Born: June 25, 1882
Resides in New Orleans
Louisiana.
Recently she appeared
in costume at Annual
Mardi Gras Ball.
Theme of the Ball:
Modes of
Transportation.

ev. Ludwig Ost
orn: October 2, 1885
oved to Nome, Alaska from Sweden in 1910.
erved in the state legislature and founded an orphanage.
oto courtesy of Sarah Jane Birdsall

Hannah Johnson Jones
Born: October 2, 1887
Moved to Manti, Utah from England in 1890.
Recalls washing clothes on a washboard and taking all day to do it.



Charlie Lowe
Born: June 23, 1876.
Resides in Phoenix, Arizona.
Photo courtesy of Laurette Alexander

hris Christiansen
orn: February 13, 1887
oved to Iowa from
enmark in 1907.
ow resides in Winner,
outh Dakota.
oto courtesy of Dan Bechtold

Marguerite Roche
101 years old.
New York City artist.
Reproduced with permission of copyright holder, M. Barcellona

Will Parks
Born: January 26, 1885
Native of Trimble, Tennessee.
As an architect he helped to design the columns of the Lincoln Memorial.
"I owe my long life to moderation in living and procrastination in dying."

Vinnie Baker Anderson
Born: January 14, 1883
Native of Vernal, Utah.
Traveled the 1986 Fourth of July Parade route on the back of a motorcycle.

Dora Zins
Born: February 25, 1884
Moved to New York from Russia in 1886.
Now resides in Silver Spring, Maryland.
Photo: Bill Branson, NIH

Ella Williams
Born: February 24, 1879
Native of Baton Rouge, Louisiana.
Attributes her long life to avoiding alcohol and men.
Photo courtesy of Ray Spruell

Frieda Hammerschlag
Born: March 9, 1882
Moved to the United States from Germany in 1941.
Now resides in Sarasota, Florida.
"Whenever I feel blue I go shopping."
Photo courtesy of Sarasota Herald Tribune

NIA Researchers Study the Role of Older People in the Changing Family

Barbara Katzman

One result of the increase in the number of older people is that many more children today than in the past personally know at least one grandparent. NIH PHOTO 2167

Quite without fanfare, a monumental change has taken place within the American family. This change came about largely as a result of increases in longevity and the tremendous growth in the number of old and very old people. More specifically, since the turn of the century, when life expectancy was less than 50 years, the number of people who have celebrated an 85th birthday has multiplied twentyfold to 2½ million people, and life expectancy at birth has increased to nearly 75 years old.

It is important to realize how this demographic change has altered, and continues to affect our society. Most older people are healthy, vital members of their communities. These people are perfectly able to do their own shopping and cooking, are engaged in hobbies and volunteer jobs, and many remain gainfully employed. Grandparenting has achieved new dimensions as many older people are involved members of multi-generational families. Yet, there often comes a time when an older person's illness or disability requires special care, usually from a relative.

Remaining Healthy and Vital

Investigators at the National Institute on Aging (NIA) and elsewhere emphasize the importance of teaching people that old age need not be fraught with disease and frailty. Contrary to what many people may believe, research findings demonstrate that older people can improve their health by practicing healthy behaviors. Additionally, we have learned that there are things a person can do throughout the life course to reduce the threat of illness and death.

Dr. George Kaplan of the California Department of Health Services has completed a longitudinal study, supported by NIA, showing that smoking cessation and maintaining appropriate weight reduce mortality rates even among the old. There are many people in their seventies and eighties who sincerely feel that if they always smoked, why stop? If they are overweight (or underweight), why change dietary habits? The truth is that research is showing that it is never too late to reduce mortality risks and increase the quality of future years by adopting a sensible lifestyle.

Dr. Kaplan found evidence that it is possible to prevent, delay, or reduce disability with preventive activities throughout the life span. To quit smoking, engage in appropriate physical activity, and maintain proper weight all help reduce the risk of death. Social isolation, defined as fewer than 5 contacts per month with family or friends, increases the risk of mortality for both younger and older people. The study provides strong evidence that by improving one's lifestyle at any age one can improve the quality of the remaining years and possibly postpone death as well.

The Role of Grandparents

One result of the increase in the number of older people is that many more children today than in the past personally know at least one grandparent. Dr. Andrew Cherlin, an NIA-supported scientist at The Johns Hopkins University, finds that the role of a grandparent has changed considerably since World War II. While grandparents of bygone days either were too frail or sick to have any real impact on the family or were strict, often feared, authoritarian figures, today's grandparents are more "companionate" and "pleasurable." Many members of multi-generation families turn to each other for comfort, support, and health care.

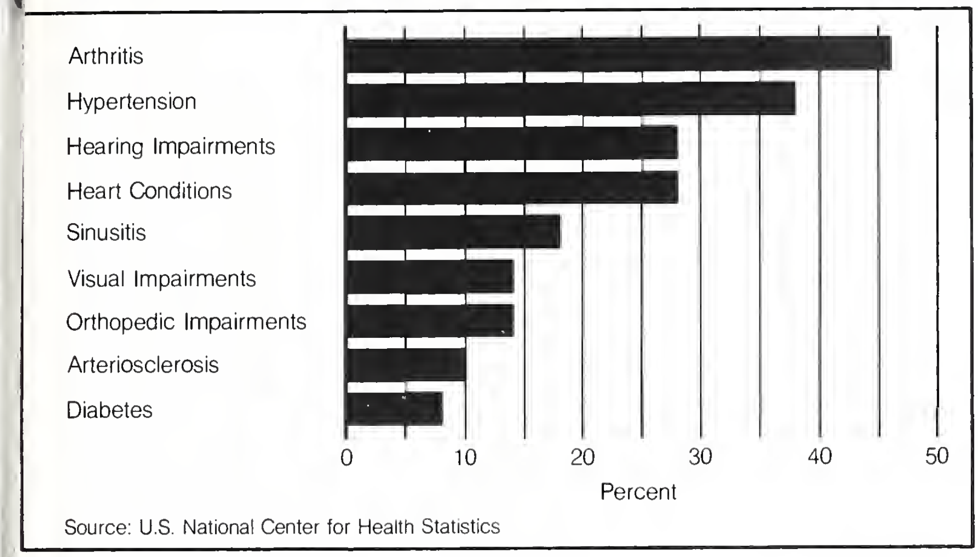
The grandparent-grandchild relationship differs somewhat in families separated by divorce. Dr. Cherlin examined the role of the grandparent in families confronted by divorce in the middle generation. He found that the role of the grandparent becomes more significant on the maternal side and will continue so as long as courts award custody most often to the mother. The role of maternal grandparents quite often becomes parental in nature while visits by paternal grandparents usually are confined to holidays and birthdays.

Dr. Cherlin hypothesizes that a closer relationship between generations is possible today because of improvements in communications and transportation. Other factors include an increase in leisure time and sufficient financial resources to permit families living great distances apart to remain close.

The support system that often exists among generations is beneficial to both the receiver of care and the caregiver. At the University of Michigan, NIA-supported scientist Dr. Robert Kahn and his colleagues investigated the positive contributions older Americans make to the family and society. He found that people between the ages of 50 and 75 often give more support to their families than they receive in return. The nature of this support includes developing mutual respect, providing reassurance, instilling confidence, and taking care of a sick relative or helping out during an emotional crisis. Additionally, grandparents often contribute financial support and frequently are called upon for child-care activities and baby-sitting services. The study emphasized that contributing useful services to family and friends encourages a positive self-image among older people.

Dr. Kahn points out that people of all ages need to have a feeling of self-worth. "The reality and experience of producing something or providing a service, and the recognition and acknowledgment of that activity as useful by oneself and others, contribute to physical and mental health." Dr. Matilda Riley, NIA's associate director

Common Chronic Conditions of Non-Institutionalized People Over Age 65



Source: U.S. National Center for Health Statistics

NIH PHOTO 2168

for Behavioral and Social Research, notes that a major priority of her program is to dispel the false stereotype that older people are "a burden rather than a resource to families and society as a whole."

When Illness Strikes

Fortunately, the view of a grandparent, or a great-grandparent, as a healthy and productive member of the family is becoming more and more common. Nonetheless, the likelihood of an older person becoming ill or disabled increases steadily with age. According to the National Center for Health Statistics, 1.4 million people over the age of 65 live with another person because of a physical or health problem. The question then becomes, "Who will provide essential care for these people?" The answer is that relatives and friends provide 80 percent of the services supplied to frail older people. A spouse or daughter is most often the primary caregiver, performing these tasks with little or no help from any other source.

The spouse is naturally the first person called upon to supply necessary care to a seriously ill mate. Ms. Kathleen Bond, NIA health scientist administrator, says, "It is not uncommon for older people to be caring for other older people. Spouses generally take care of each other at any age. Very old people often are cared for by their aging children." The National Center for Health Services Research has estimated that about one-third of those who care for elderly relatives are themselves over the age of 65.

When a child is the caregiver, it is most often a daughter or daughter-in-law. At the University of Massachusetts, NIA-supported scientist Dr. Alice Rossi says that, "Today's middle-aged adults have fewer adult siblings to share social and emotional, if not financial, responsibility for elderly parents who are living to old-old age in unprecedented numbers." NIA-supported scientist Dr. Gunhild O. Hagestad at the Pennsylvania State University explains that daughters naturally step into caregiving roles because of early socialization of female roles which encourage strong family ties and kinships.

Providing care can be difficult. Twenty-seven percent of the informal caregivers responding to the Department of Health and Human Services (DHHS) Long Term Care Survey reported that they are unable to leave their elderly disabled relatives alone at home. Fifty-four percent of adult children caring for their elderly disabled parents reported that their social life or free time was limited by caregiving; 26 percent reported lessened privacy; and 28 percent said that their elderly disabled parent required almost constant attention. Social and emotional losses and sacrifices were reported more frequently than financial strain.

Providing care to a sick relative or friend is made all the more difficult when juggling the additional demands of employment. An independent study conducted by Travelers Insurance Company found a high frequency of caregiving among employees. In fact, results indicated that 20 percent of their employees spent an average of 10.2 hours a week caring for a relative or friend who was over 55 years of age. Eight percent devoted 35 hours a week to such care. Nearly half of the caregivers in the sample indicated they were the primary caregiver who provided services ranging from visits and phone calls, to performing household chores, to managing the person's finances. The survey also concluded that caregivers usually experienced a great deal of stress while coping with the additional responsibilities of caring for an older person. Eighty percent of the caregivers responded that caregiving interfered with their social and emotional needs and with other family responsibilities.

NIA-supported scientist Dr. Rosalie Young at Wayne State University conducted a study on the effects of caring for seriously ill patients recovering from a heart attack. Though the study was on a relatively small sample, Dr. Young found that caring for a seriously ill person requires between 3 and 5 hours each day of meal preparation, grocery shopping, housework, laundry, transportation, and other activities. Caregivers also supply financial support, medical assistance, and help with such personal needs as bathing, toileting, and dressing. Initial results of the study indicate that caregiving does present adverse physical and psychological effects on up to 37 percent of caregivers.

Care Provided	% of Caregivers Providing Care
Companionship (visits and phone calls)	76%
Provide transportation	62%
Perform household chores	57%
Manage finances	44%
Arrange/coordinate outside assistance	36%
Provide direct financial support	30%
Assist with personal care	13%
Administer medication	11%

—from The Travelers Employee Caregiver Survey

Dr. Young found that "caregivers can, and often do, perceive their activities in a negative manner." The greatest negative impact was on family life—62 percent of caregivers who had to alter their schedules did so by cutting back on family related activities. When considering non-spouse support, one-fourth of the caregivers in Dr. Young's study indicated that it was difficult to find adequate time to spend with their children. Most caregivers find it difficult to balance time, effort, and emotional commitment encountered as a result of their new role. Other studies substantiate the difficult role of the primary caregiver who often is the sole source of support for a chronically ill person.

Future of Caregiving

Caregivers, for the most part, are thrust into their new role with no adequate preparation and no time to learn what is required, what an older persons feels, or what their own needs might be. The time, effort, and personal stress encountered in such everyday care often are overwhelming.

In research currently supported by the NIA, Dr. Elsie Pinkston at the University of Chicago has studied the possibility of teaching families how to adjust to their new role and to relax some of the tensions and stresses of caregiving. Termed the Elderly Support Project, the study was designed to evaluate different techniques and procedures that families use in home care and subsequently alter traditional methods to better meet the needs of each family member. Dr. Pinkston found that by teaching sick older people certain self-care techniques, many could perform more tasks on their own. The ultimate goal is to increase the independence of older persons, thereby delaying or eliminating the need for nursing home care.

As a result of this project, caregivers found their health and stress levels improved. Dr. Pinkston is expanding the scope of her project to include assistance to families in the Chicago community. Such programs may eventually be available to provide families in all parts of the United States with assistance in coping with an ill or frail relative.

Our circle is now complete. From the tremendous number of older people who are enjoying family relationships never deemed possible in decades past, to the potential difficulties which illness can impose upon family members, creative methods can be devised to better meet the needs of every member of the family.

Grandparents are the link to past generations—the primary source for carrying on family rituals and traditions. Never before has society had to respond to the needs of such a large older population. As NIA director Dr. T. Franklin Williams appropriately states, "It is time for society to stop thinking in terms of what we will do for older people and concentrate on what we can do with older people." Society will be ever so much richer as a result. ■

"I look back on my life like a good day's work, it was done and I feel satisfied with it. I was happy and contented, I knew nothing better and made the best out of what life offered. And life is what we make it, always has been, always will be."

Anna Mary (Grandma) Moses

Sensory Changes that Occur with Age Investigated at GRC

Jan Ehrman

Changes in sensory functions appear to mimic other physiological alterations that occur with age. On the average, declines for both visual acuity and hearing thresholds are seen in older age groups; however, the amount of decline is remarkably variable among individuals, according to recent findings from a long-term study at the National Institute on Aging's (NIA) Gerontology Research Center (GRC) in Baltimore.

Findings taken previously from the 29-year-old Baltimore Longitudinal Study of Aging (BLSA) have demonstrated that aging usually results in a gradual, albeit individualized, set of changes, usually declines, for most organ functions. For example, renal function may decline 30 to 50 percent in many persons between the ages of 30 and 80. However, the declines or differences observed among healthy individuals vary dramatically and this gap widens further with time; some persons seem to show no declines at all.

While much has been learned about changing physiology across the lifespan, not that much is known about long-term changes in sensory function. Most studies conducted previously in these areas have been cross-sectional, that is, in which persons of different ages are studied one time. A limitation of this type of research is that results may represent characteristics specific to the subjects in that study, but not to the aging population as a whole. One way to overcome this is to follow age changes in one group as its members age. This is being done by NIA scientists at the Baltimore facility, who have recently focused on age-related changes in hearing and vision among their cohort of healthy subjects.

In general, the majority of people experience some diminution in visual perception after age 40. By age 80, less than one out of five men and women have 20/20 vision. Further, 30 percent have poorer than 20/100 vision, meaning they can see at 20 feet what the average-sighted individual, or someone with 20/20 vision can interpret at a distance of 100 feet.

These results emerge, in part, from a 10-year longitudinal analysis conducted at the GRC to assess near and far visual acuity (sharpness) in 587 males in the BLSA. The subjects, who ranged in age from their twenties to their eighties, were tested at least seven times over a 14-year period with a Titmus testing device (similar to the one used for driver's license tests).

According to the investigators, Mr. Neil Gittings, Dr. James Fozard, and Dr. Nathan Shock, who reported their findings in *Experimental Gerontology* (vol. 21, nos. 4/5, 1986), modest declines in acuity were observed across the entire age spectrum for subjects with both corrected and uncorrected vision. The researchers said that most major changes occurred in men who were in their sixties and seventies when first tested.

Uncorrected near acuity declined significantly for BLSA participants between the ages of 40 and 50, reflecting the loss of accommodation that becomes noticeable in that age range. Loss of accommodation, which occurs due to changes in the structure of the eye's lens, results in poorer visual acuity for reading printed matter.

Additionally, BLSA results indicated that greater losses in visual acuity occurred among subjects with better initial acuity. Those demonstrating poor acuity on the first test typically remained the same or improved minimally. Further, acuity was slightly altered by self-reported glaucoma or retinal pathologies and to a greater extent in persons with lens opacities, or cataracts.

In the past, cross-sectional investigations have confirmed an incidence of gradual hearing loss, known as presbycusis. Though these age-associated deficits often begin after age 30, symptoms may not become apparent to those afflicted until years later. Presbycusis affects twice as many men as women.

Scientists at the NIA/GRC have conducted longitudinal analyses of hearing thresholds of several hundred BLSA volunteers and have been able to document age changes for the first time. Their results demonstrate that 10-year age changes in hearing thresholds occur in *all* age groups from the twenties to the eighties. In addition, the degree of change in 20 and 30-year-olds was greater than was previously believed.

Although the BLSA investigation confirms previous findings that the age-associated loss is greatest in the ability to perceive high-pitched sounds, it shows that "normal" hearing loss occurs over the entire frequency spectrum, according to Dr. Larry Brant, Mr. Jim Wood, and Dr. James Fozard. The problem may result from degenerative changes in the inner ear, some experts contend.

A loss of hearing also can lead to added complications. It may affect speech intelligibility, may contribute to socioeconomic problems, or, in rarer cases, may lead to emotional disorders, such as paranoia or other conditions yielding a high degree of distrust in others.

While GRC investigators probe into the many mechanisms that may be responsible for the human body's changing physiology, their research is providing a better understanding of the significance of age-related vision and hearing loss for everyday functioning. ■

BLSA subject undergoes testing in soundproof hearing chamber at the GRC in Baltimore. Studies at the Center indicate that age changes in hearing thresholds occur in virtually all age groups across the life span.

Photo courtesy of Photography and Arts Unit, GRC, NIA. NIH PHOTO 2169

Studies Identify Older Persons at Risk of Falling

Virginia Morgan

Falls result in a large number of hip fractures each year and are the most common cause of fatal injury in older persons. Two recent studies conducted by NIA-supported scientists identify primary causes of many falls as well as ways to prevent them.

Of more than 200,000 hip fracture hospitalizations each year, 84 percent involve persons over age 65. Twenty percent of persons who fracture a hip die within a year of the injury. Other serious accompaniments of hip fracture injuries are pain, long periods of hospitalization and recovery, loss of independence and mobility, and institutionalization. The fear of falling again in the future causes many people to become inactive or to avoid, sometimes unnecessarily, situations they feel may lead to a fall.

Older persons are especially likely to fall. A fall can result from poor hearing or vision, impaired balance and coordination, or multiple use of drugs—all characteristics common to the elderly population. Falls are sometimes the first symptom of a serious illness (such as heart or brain disease).

In a study analyzing falls and fall injuries that occurred in nursing homes, Professors Susan P. Baker and Ann H. Myers at The Johns Hopkins University in Baltimore found the average resident fell twice during a 1-year period; and while 70 percent of these falls caused no injury, the other 30 percent resulted in injuries ranging from fractures (2.4 percent) to sprains, bruises, and cuts. Sixty-four percent of falls occurred during daytime hours and 20 percent were witnessed by another person. One and one half percent of falls resulted in fractured hips, with women three times more likely than men to suffer such a fracture subsequent to a fall.

The 3-year study by Baker and Myers was directed in part at developing a screening tool to be used by nursing home staff to identify characteristics of persons at high risk of falling. It was believed that the careful surveillance of high-risk patients viewed in relation to common factors associated with falling (e.g., environmental obstacles, the use of medications, and medical diagnosis) might help identify factors that could prevent future accidents or could at least reduce fall injuries.

In a second study, Dr. Mary E. Tinetti and colleagues at the Monroe Community Hospital in Rochester, New York, examined the relationship between falls and number of disabilities of each person—such as declines in mobility, mental status, distance vision, hearing, back flexibility, and leg strength. Multiple use of medications was also considered a disability.

Ambulatory residents of an intermediate care facility in Rochester were evaluated for the occurrence of falls as well as presence of high-risk disabilities. (An intermediate care facility provides institutional care and services to individuals, although not to the degree these are provided in hospitals and nursing homes.) The results demonstrated that as the number of disabilities rose, so did the likelihood of falling. No one with three or fewer disabilities fell more than once during the study period, whereas every person with seven or more disabilities fell two or more times. And those with an intermediate number of disabilities had an intermediate chance of falling.

Almost all recurrent fallers had poor back flexibility, decreased strength in the lower extremities, and poor distance vision. Other characteristics associated with recurrent falling were a decrease in mental status, hearing problems, poor endurance, reduced knee strength, and a significant drop in blood pressure when standing up.

The two studies suggest an inadequacy in the usual medical approach to falling, which is often limited only to ruling out such causes as seizures. Potential fallers can be identified with greater accuracy by using simple tests of balance and gait, combined with knowledge of routine data obtained during medical examination. (Examples of balance and gait deficits are difficulty in rising or sitting down, instability when first standing, staggering when turning, and short discontinuous steps.) ■

TIPS FOR PREVENTING ACCIDENTAL FALLS

The likelihood of falling can be reduced by taking precautionary measures, for example:

To avoid becoming dizzy when standing up, rise slowly from a sitting or lying position.

Provide ample lighting throughout the house, especially next to bedside tables and in halls and stairways.

Install hand rails along both sides of a stairway to help break a fall.

Clearly mark the first and last step with a bright, contrasting tape.

Check that floor surfaces throughout the house are even and free of clutter.

Cover slippery surfaces with carpets or rugs that are in good repair and firmly anchored to the floor; attach nonskid rubber backing to area rugs.

Use a nonskid floor wax on linoleum floors.

In bathtubs use nonskid adhesive strips or plastic mats.

Install grab bars on bathroom walls.

Arrange furniture so that it doesn't create an obstacle.

Landmark Study Charts Healthy Older People

Barbara Katzman

A unique book about older people has been released recently by The National Institute on Aging (NIA). The *Resource Data Book* contains baseline results from an ongoing landmark study that focuses on the health and behavior of people over the age of 65 living in three communities in the United States. What makes this study so unique is that it represents the first large-scale, community-based, epidemiological study of older people.

"The study, "Established Populations for Epidemiological Studies of the Elderly" (EPESE), contains information gathered from more than 10,000 participants in three rather diverse communities: New Haven, Connecticut; East Boston, Massachusetts; and Iowa and Washington counties, Iowa. (A fourth community, Durham, North Carolina, was added in 1984 to provide information on a 50 percent black population. Results of this Durham study are not yet available.)

Among interesting facts contained in these baseline findings: a majority of the participants reported some hearing loss yet an overwhelming number never used a hearing aid; women experienced a greater number of sleep disorders than did men, primarily wakefulness during the night and sleepiness during the day; and at the time of these baseline interviews about 14 percent of the woman age 85 and older had reported a history of nursing home care compared to 8 percent of the oldest men.

East Boston is located on an island in Boston Harbor. Though an ethnically diverse community, the predominant ethnic group is Italian. East Boston is basically a blue-collar community, consisting of low- and middle-income working class people. Principal investigators Drs. James Taylor and Denis Evans use the facilities at the East Boston Neighborhood Health Center, the Channing Laboratory, Brigham and Women's Hospital, and Harvard Medical School for their research.

New Haven is the third largest city in Connecticut. Residents generally are employed by educational institutions or manufacturing and service industries. The per capita income of New Haven is well below the median for the state. Among the older people the predominant ethnic group once again is Italian. About 19 percent of the population 65 and over in New Haven are black. Principal investigators Drs. Adrian M. Ostfeld and Lisa Berkman are conducting this study at the Yale University Department of Epidemiology and Public Health.

Iowa and Washington counties, two rural areas in the central part of Iowa is the third area targeted for study. Agriculture is the primary source of income but light industry and tourism are other sources of employment. Drs. Robert B. Wallace and Frank Kohout are conducting this study at the University of Iowa Department of Preventive Medicine and Environmental Health.

The value of this research lies in its prospective design—following the same persons over several years. The studies provide us with statistical information on changes which commonly accompany the aging process, such as retirement, bereavement, illness, and disability, as well as nursing home placement. Such varied factors as alcohol consumption, family interaction, and the use of medical and dental care services are being studied in relation to health conditions, mortality, disability, and institutionalization. Findings from EPESE may make it possible to answer some of the questions about the quality of life for the roughly 29 million older people in the United States. Such questions include: How dependent are older people on family and friends? How often do they seek medical and dental care? How limited is their physical condition? What can be done to encourage healthier lifestyles?

This represents only the first stage in the EPESE project—namely the collection of baseline prevalence data—and follow-up data will establish the incidence rates. Dr. Joan Cornoni-Huntley, deputy associate director of Epidemiology, Demography, and Biometry at the National Institute on Aging (NIA) believes that the "information will be of great benefit to health care professionals and policy makers planning for the future needs of our older population."

Copies of the *Resource Data Book* were made available to libraries in Medical Schools and Schools of Public Health across the country. ■

Editors of publications may request a glossy print of the numbered photographs appearing in this issue.

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July 1987

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Special Issue:

Women's Health

A Century of Progress
and Future Challenges

WOMEN'S HEALTH

Vol. 88, No. 1, August 1988

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NEWS & FEATURES
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Introduction

"Women must be willing to take charge of their own health, to become educated, to be determined to adopt healthy habits, and to be able to take full advantage of the benefits of modern biomedical research."

Ruth L. Kirschstein, M.D.

Since its beginning a century ago as a small attic laboratory, the National Institutes of Health (NIH) has applied the methods of scientific research to many problems that have a direct impact on the health of American women.

In 1887, the primary health concern was infectious disease, particularly yellow fever, cholera, diphtheria, and smallpox. Pneumonia and tuberculosis were major killers.

"These infectious diseases obviously had a great impact on women's health," says Dr. Ruth L. Kirschstein, M.D., director of the National Institute of General Medical Sciences. "While microorganisms showed no gender preference, women were still at a great risk of death from infection during childbirth."

In the late 1880's biomedical researchers were beginning to develop ways to identify the microorganisms responsible for specific infectious diseases. The NIH started, as the Laboratory of Hygiene on Staten Island, N.Y., in the hope that science could control these serious problems.

From these beginnings came the progress in research that led to the prevention and elimination of so many afflictions that struck down mothers and children in large numbers. Pneumonia and tuberculosis are no longer death sentences, and many other major infectious diseases that threatened life at the turn of the century are now under control. The discovery of antibiotics was critical in making many of these advances possible, including contributing to the decline in the maternal death rate. In addition, in the last half century the widespread use of vaccines has brought under control a host of childhood diseases that once ravaged the younger population.

Since then, research in areas other than infectious diseases has also contributed to improving women's health. In recent decades an increased understanding of the reproductive process has given women unprecedented control over childbearing. Contraceptive techniques and new methods for dealing with infertility have allowed many women the freedom to plan their families as they choose. Improved nutrition and better techniques for detecting and treating birth defects have greatly increased the chances for women to bear healthy babies.

Progress has also been made against a number of diseases that predominantly affect women. The development of mammography and self-examination techniques has helped detect breast cancer at earlier, more treatable stages. Use of the Pap smear has likewise helped detect cervical cancer earlier and improve survival rates. Systemic lupus erythematosus, which strikes women nine times more often than men, has been reduced from an almost always life-threatening disease in the 1950's to a usually controllable chronic condition.

Furthermore, the advances of the past century have translated into increased longevity. Far fewer children are dying in infancy. A century ago the infant death rate was almost 16 percent of live births, while today it is closer to 1 percent. And, a woman born today can expect to live 78 years, compared with only 48 if she had been born in 1900.

Despite a century of progress in women's health, American women face new challenges. Early this century heart disease surpassed infectious diseases as the leading killer of women, and still remains so. Among women ages 35 to 54, cancer has now become the leading cause of death due, in part, to the rise in lung cancer. This cancer has been increasing rapidly among women since the 1960's and is expected to continue to increase into the next century because of the large number of women who have started smoking in the past 30 years.

The sexual revolution that began in the 1960's has led to a host of new health problems, especially for women. American girls are becoming sexually active at younger ages, leading to the growing problem of teen pregnancies. Sexually transmitted diseases, such as chlamydial infection and other causes of pelvic inflammatory disease, are also on the rise. And AIDS, or acquired immunodeficiency syndrome, which is at this time more prevalent in male homosexuals and intravenous drug abusers than in the general population, has become a small but growing threat to certain heterosexual women.

The "graying" of the American population, coupled with the fact that women generally outlive men, means that more women will face the problems that may come with old age. Osteoporosis puts older women at higher risk for debilitating fractures. The prevalence of Alzheimer's disease increases with age, as does the problem of incontinence.

However, Dr. Kirschstein believes there is much hope. "A crucial element in disease prevention is an educated public. Women must be willing to take charge of their own health, to become educated, to be determined to adopt healthy habits, and to be able to take full advantage of the benefits of modern biomedical research," she says. "We may then be able to eliminate some of today's major health problems—just as many of the health problems of the 19th century are now eradicated or controlled."

It is toward a better educated public that the NIH presents this special issue of "News & Features", celebrating the progress in women's health over the past century and looking to the promises and needs of the future. ■

Vaccines Against Childhood Diseases

On May 14, 1796, English physician Edward Jenner inoculated a young boy with cowpox virus, which causes only mild illness, to protect him from much deadlier smallpox. Since that first vaccination nearly two centuries ago, the smallpox scourge has been eliminated entirely from the world, and the incidence of many other devastating diseases—especially those of children—has been greatly reduced.

Today, more than a dozen vaccines have been developed that have dramatically improved the health and well-being of children and adults throughout the United States. Because of these vaccines, U.S. health officials could report in 1982:

—just three cases of diphtheria, compared with more than 200,000 in 1921.

—only 1,700 cases of pertussis, or whooping cough, compared with 26[illegible],000 in 1934.

—only 1,700 cases of measles, as opposed to 894,000 in 1941.

—just seven cases of paralytic polio, compared with 21,200 in 1952.

Vaccines against childhood diseases have also greatly influenced the lives of women. As the primary caretakers of children, women shoulder the greatest burden of caring for sick youngsters. Vaccines have freed women from much of the burden of child sick care, contributing tremendously to their psychological and physical well-being as well as to the economic wealth of those women who could now more easily work outside the home. In addition, vaccinated mothers protect their unborn babies from infections that can be passed to them in the womb.

Since its beginning as the Laboratory of Hygiene in 1887, the NIH has supported basic research into infectious diseases and, later, into the development of vaccines and their evaluation. Since 1948, when the National Institute of Allergy and Infectious Diseases (NIAID) was founded at NIH, much progress has been made in developing vaccines against childhood diseases. NIAID-supported research has contributed to the development and evaluation of new or improved vaccines for measles, rubella, hepatitis B, pneumococcal pneumonia, adenovirus-caused respiratory disease, and *Haemophilus influenzae* type b meningitis. The first three are especially significant for women.

Measles

"Measles is probably the most important of the childhood diseases," says William Jordan, M.D., former director of the Microbiology and Infectious Diseases Program at the NIAID. Before vaccines, measles touched an estimated 95 percent of Americans by age 15. Should a pregnant woman get it, measles can lead to miscarriage, premature labor, or low birth-weight babies and, possibly, to birth defects.

In the 1950s, NIAID expanded support for basic research on growing viruses in cell culture. Scientists then isolated the measles virus, developed weakened viral strains for a vaccine, and tested the vaccine's safety and effectiveness. Since the licensing of a live measles vaccine in 1963, childhood vaccination programs have reduced the reported incidence of measles by 99 percent.

For those who do get measles, though, the disease is still serious. It is often complicated by middle ear infection or pneumonia. Infection of the brain, or encephalitis, occurs in about one of every 2,000 cases reported. About a quarter of the children who survive encephalitis may have brain damage resulting in seizures, deafness, or mental retardation. Measles kills about one of every 3,000 children who develop the disease.

With mandatory vaccination of all school-age U.S. children, measles now occurs primarily in young women and men. Many of these people were born around the time the vaccine was introduced. They may have missed being vaccinated or may have been vaccinated in their first 15 months, an age where the vaccine was sometimes not effective.

Rubella

Like measles, rubella—or German measles—occurs primarily in preschool children and young adults who have not acquired immunity through vaccination or an earlier case of the disease. Unlike measles, rubella is usually a very mild illness. But it is a serious concern to young women who become pregnant, due to severe effects on the unborn child.

"If the expectant mother is infected early in pregnancy, the results could be devastating," Jordan said. "She delivers a deaf, blind, or mentally retarded child." These complications are called congenital rubella syndrome (CRS). Intrauterine infection can also result in stillbirth or miscarriage.

The rubella epidemics in 1935, 1943, and 1964 dramatically affected babies born then. In the 1964–65 worldwide epidemic, 125 million cases of rubella resulted in 20,000 infants born with CRS,

Vaccination protects children from serious infectious diseases. Many vaccines now available are the result of research supported by the National Institute of Allergy and Infectious Diseases (NIAID).

which killed one out of 10 within a few months of birth. More than half of the CRS infants were born deaf. The economic impact of this epidemic was estimated at $1.5 billion.

The rubella virus was finally isolated in the early 1960s by NIAID-supported scientists and by scientists at the Walter Reed Army Institute of Research. Subsequent NIAID-supported research aimed at developing weakened viral strains for a vaccine, its testing and evaluation. A live vaccine was licensed in 1969.

Hepatitis B

Hepatitis B is another important viral illness that can be passed to newborn infants. It is a liver disease that affects millions of people worldwide. It is usually an acute illness from which patients recover in several weeks without damage to the liver. However, in about 10 percent of the patients, the virus continues to grow, turning them into virus carriers. And women who carry the virus can transmit it to their babies.

"We don't know how it's passed," Jordan said. But "it seems to be from close contact at birth or in the first few months." The virus is perhaps passed through vaginal or cervical secretions. It is so common in a few countries outside the United States that health officials assume every newborn has it.

Scientists do know that, between adults, the virus can be transmitted by blood, semen, or saliva. In the United States, it is most commonly passed by sexual contact and intravenous drug use. The infected who become virus carriers are at risk of chronic active hepatitis, a condition that can damage the liver and lead to cirrhosis, liver failure, and perhaps liver cancer.

About 1 million Americans carry the hepatitis B virus, which infects an estimated 200,000 others each year. About 37 percent of the infected are women. The disease hospitalizes more than 16,000 in the United States every year, and severe infection takes an average of 250 lives. Chronic liver disease resulting from hepatitis B kills another 5,000 annually. The economic impact of the disease has been estimated as high as $1 million a day in this country. There is no effective treatment for the illness, but it can be prevented.

In 1963, Baruch Blumberg at the NIH's then National Institute of Arthritis and Metabolic Diseases (NIAMD) discovered a hepatitis B protein, initially called the Australia antigen, which is part of the virus that causes the disease. (In 1976 Blumberg shared a Nobel Prize for his work on the antigen.) Since the discovery, NIAID has conducted and supported research on this virus and contributed to the development of a vaccine licensed in 1981. Results of NIAID-supported research on the vaccine given newborns at birth have demonstrated that it does prevent hepatitis B infection. Protection is even greater when a dose of immune serum is given to protect the infant while it develops vaccine-induced immunity. The vaccine and immune serum are only given to infants whose mothers might be carriers.

The NIAID is continuing to support the evaluation of recombinant hepatitis B vaccines, which might cost less than current vaccines. The Institute is also supporting research on other vaccine approaches, such as synthetic peptides and anti-idiotype antibodies, which might be just as effective but with fewer side effects.

An NIAID accelerated program is also developing improved vaccines for pertussis, pneumococcal pneumonia, and *Haemophilus influenzae* type b meningitis as well as new vaccines for chickenpox, croup in infants, and infant diarrhea caused by rotaviruses. In addition, NIAID is investigating vaccines against sexually transmitted diseases, such as gonorrhea, genital herpes, and chlamydia, that can be passed to newborns.

Through this vaccine research, many of the infectious diseases that disable children and affect the economic, psychological and physical well-being of women may one day be prevented. ■

Before widespread vaccination, about 95 percent of Americans had measles by age 15. In the Third World, an estimated 67 million cases occur annually, causing 2 million deaths.

Sexually Transmitted Diseases

The cloud of public concern over AIDS, or acquired immunodeficiency syndrome, has virtually obscured the epidemic problems of other sexually transmitted diseases in the United States during the past half dozen years. The situation is especially serious for women. Health complications caused by STDs tend to be more frequent and more severe in women than in men. In addition, they may result in infertility, chronic disease, cancer, or death as well as abnormal pregnancies and harm to infants before or after birth.

Twenty-three STDs and a dozen STD syndromes affect more than 10 million women and men in this country every year. The U.S. Surgeon General has designated STDs a priority for prevention and control efforts as part of the nation's health objectives for 1990.

STD outbreaks have been recorded throughout history, but today new factors are also at work. The "baby boom" has placed an increased proportion of the U.S. population in the age group where STDs are most common. Women are at higher risk for STDs now because they often become sexually active at younger ages, have more than one sex partner, or change partners frequently. The emergence of drug-resistant microbes has contributed to the difficulty of controlling gonorrhea. And, undoubtedly, improved diagnostic tests have led to higher reports of STD occurrence.

The most important STD among American women today is called pelvic inflammatory disease, a general term for inflammation in the female genital tract. PID is caused by a number of microorganisms and can produce chronic pelvic pain, infertility, or tubal pregnancies.

"PID has only been recognized in the last five years or so as being a problem," said William Allen, Ph.D., chief of the Bacteriology and Virology Branch of the Microbiology and Infectious Diseases Program of the National Institute of Allergy and Infectious Diseases (NIAID). The syndrome affects an estimated 1 million women in the United States every year and totals more than $2.5 billion in direct and indirect costs.

PID is most often caused by gonococcal or chlamydial infection, and about 10 to 20 percent of women with either of them develop acute PID. Unrecognized PID resulting from increases of these infections in the 1960s and '70s probably contributed to the three-fold increase in tubal pregnancies in the United States since 1970.

Women face greater risk of PID if they have multiple sex partners or, possibly, if they use an intrauterine device for birth control. Oral contraceptives, on the other hand, can have a slight protective effect.

Treatment of PID is complicated by the many microorganisms that can be involved. Several drugs may be needed since one might not be effective against all the organisms. Last year the NIAID funded research units in Boston, Seattle, and San Francisco to further investigate the syndrome.

Chlamydial infections, caused by the bacterium *Chlamydia trachomatis,* are now the most common of all STDs in women. The number of new cases has increased to an estimated 4 million per year and is still rising. In addition to possibly leading to PID, chlamydial infection may cause pain in the abdomen, a discharge from the vagina and itching or burning in the genital area, especially during urination. Until recently, these infections were very hard to diagnose due to the difficulty of growing chlamydial bacteria in the laboratory for diagnostic tests. But in 1985, NIAID-supported scientists developed a test using monoclonal antibodies, which can be made in large quantities in the laboratory.

Chlamydial infections can occur without symptoms and still do damage. One NIAID-supported study suggests that a substantial number of symptomatic women may have not only chlamydial infection of the lower genital tract but also of the upper genital tract where chronic, undiagnosed infection causes infertility and tubal pregnancy.

Chlamydial infections are treated with antibiotics, such as tetracycline. The cost of health care for the infections now approaches $1.5 billion a year.

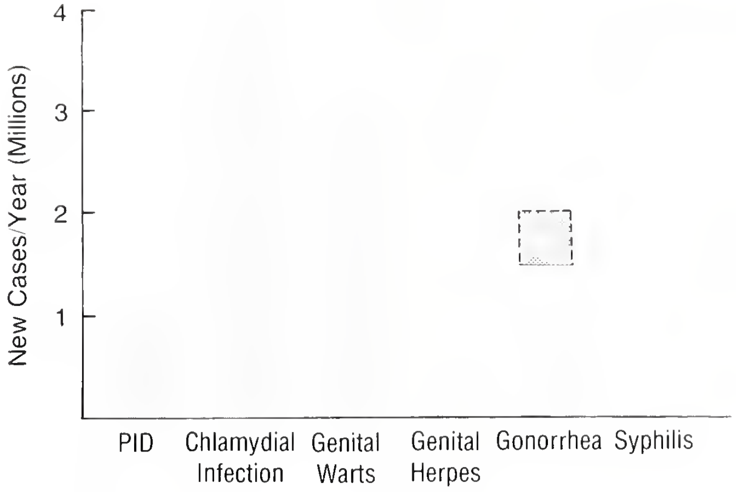
After PID, the most important STD in women today is genital warts. They are caused by the human papilloma virus (HPV). Certain strains of this virus have been associated with the development of cervical cancer.

HPV infects up to three million American women each year, but many more may be infected without knowing. Between 5 and 10 percent of college women have been found during annual examinations to have HPV infection of the cervix.

Genital warts are generally treated with a drug applied on the surface or by freezing, but they can grow back. Large warts can be removed by surgery.

HPV can be transmitted from mother to infant at birth, and NIAID scientists are investigating how it happens. HPV infection in infants and children can cause warts to grow in the throat and respiratory tract, sometimes blocking the air passage. Even when these warts are surgically removed, they sometimes grow back.

SEXUALLY TRANSMITTED DISEASES



Number of cases per year of some of the major sexually transmitted diseases affecting American women.

Genital herpes, caused by the herpes simplex virus (HSV), increases by half a million cases a year in the United States and now afflicts an estimated 30 million Americans. Statistics from the Centers for Disease Control suggest that 30 to 35 percent of the U.S. population has been exposed to the virus.

Painful blisters or open sores in the genital area are the major symptoms of herpes infection. The sores usually disappear in two to three weeks, but the virus remains in the body and the sores may recur from time to time. Subsequent episodes are not usually as severe as the first.

An NIAID scientist has found that herpes can be transmitted between sexual partners even when the infected partner does not have symptoms. The virus can also be passed to an infant during birth, which can lead to a variety of problems, including encephalitis. Doctors can deliver a baby through Caesarean section to avoid herpes infection if the mother shows signs when the infant is due.

Genital herpes is now treated with acyclovir, an antiviral drug available by prescription. The drug helps control symptoms but does not eliminate the herpes virus from the body. Patients with frequently recurring herpes outbreaks can suppress them in 60 to 90 percent of the cases by using oral acyclovir continuously for several months.

Cytomegalovirus (CMV) is a common member of the herpesvirus family that usually causes only mild infection in adults. Congenital CMV infection occurs in about one percent of live births and often causes severe developmental defects and mental retardation. NIAID is funding research into ways of preventing CMV transmission at birth.

Today many STDs have reached epidemic proportions among women in the United States. Research investigators supported by NIAID are searching for better methods of diagnosis, better treatments, and more effective vaccines for them. One day they hope to ensure that these diseases, like so many other infectious diseases, will no longer pose a serious threat to women's health. ■

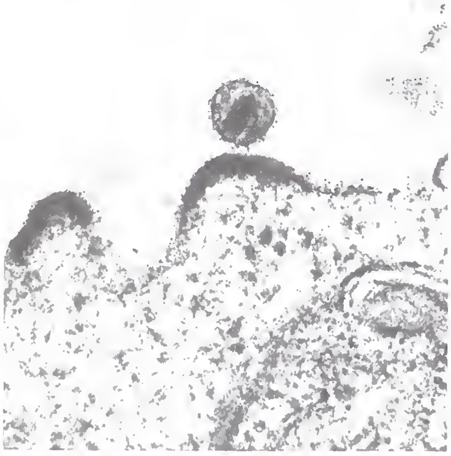
AIDS in Women

AIDS, or acquired immunodeficiency syndrome, has become an increasingly larger threat to the health of women—especially ethnic minority women—in the United States since the disease was first described in 1981.

Today AIDS afflicts nearly 3,000 women, more than 70 percent of them black or Hispanic. The disease has become epidemic in a few cities, such as New York, where in 1986 it was the leading cause of death among women age 25 through 34.

Half the women with AIDS became infected with HIV, the human immunodeficiency virus that causes AIDS, by using contaminated needles when taking intravenous drugs. But a growing and worrisome number are becoming infected through sexual contact with men who carry the virus. Today 30 percent of infected women became infected through heterosexual relationships, more than double the rate five years ago.

"There is a real danger to women," said Harold Ginzburg, M.D., chief of the Epidemiology Branch of the AIDS Program at the National Institute of Allergy and Infectious Diseases (NIAID). "Until recently, the focus has been on male homosexuals, so women tended to take (the threat of AIDS) lightly. And they have not been taking steps to protect themselves."



Electron micrograph showing the AIDS virus budding from a T cell.

Ninety-three percent of American adults with AIDS are male, and nearly four out of five of them contracted the disease through homosexual or bisexual relationships. AIDS remains a deadly disease. There is still no cure and no proven vaccine against it. AIDS has struck more than 42,000 Americans, killing 60 percent of them. AIDS virus has infected more than a million, and up to half of them are expected to develop the disease.

Pregnancy seems to worsen the symptoms of AIDS. Infected pregnant mothers appear more susceptible to the development of AIDS. Pregnancy may—but it is by no means certain—influence the progression of HIV infection toward AIDS in women who, until then, showed no sign of disease.

Pregnancy does, however, put the infant at great risk of HIV infection and AIDS. An overwhelming majority of the 580 American youngsters with AIDS were infected with the virus from their mothers. A number of studies and cases suggest that a woman can pass the virus to her infant in the womb, during birth, or while breast feeding. An estimated 30 to 50 percent of children born to HIV-infected mothers will have the virus. But no one is certain how many of these babies will eventually develop AIDS.

The only way an infected woman can be certain not to pass HIV to her infant is not to get pregnant. Because this virus can reach a baby in the uterus, mothers with HIV cannot rely on having an uninfected child by delivering it through Caesarean section, the procedure sometimes used to avoid infecting the infant of a woman with genital herpes. Women thinking about getting pregnant—and 80 percent of women with AIDS are of childbearing age—should be screened for HIV if they are at risk of carrying the virus. Those at risk are women having sexual contact with men who might carry HIV; women with other sexually transmitted diseases; or women from countries, such as Haiti, where heterosexual transmission of HIV is common. Prostitutes and intravenous drug users are at very high risk.

The only way women can be absolutely certain of not getting HIV—and possibly AIDS—is to refrain from activity involving the exchange of body fluids, such as blood, semen, or saliva. The risk of passing HIV through oral sex or kissing appears low but is unknown. Anal intercourse clearly presents the greatest risk of passing HIV. Scientists have not yet established the degree of risk from vaginal intercourse nor the efficiency of intercourse in passing the virus. However, men seem to pass HIV more easily to women—perhaps because women receive semen—rather than the reverse.

Dr. Wayne Greaves, Chief of Infectious Diseases at Howard University in Washington, D.C., is involved in the epidemiology—study of the various factors that determine the distribution and frequency of diseases—of AIDS in the United States and in developing countries. He is also a member of the NIH AIDS Research Review Committee and has spoken on the effects that AIDS is having on the Black community.

AIDS research at NIH is coordinated by NIAID. That institute and the National Cancer Institute (NCI) lead the investigation into the basic science of AIDS as well as the development and testing of new treatments and vaccines. Since 1983, NIAID has studied the natural history of AIDS in a homosexual population of 6,500 men in five cities. The NIAID, together with the Centers for Disease Control, is also conducting natural history studies in Africa, where AIDS afflicts equal numbers of men and women. In 1984, Dr. Robert Gallo at NCI identified HIV as the cause of AIDS.

In 1985, an NCI screening program found that the drug AZT, or azidothymidine, could reduce the symptoms in some AIDS patients. The Cancer Institute conducted the first of the clinical trials leading to Food and Drug Administration approval of AZT for general use. In 1986, NIAID established the first of 16 centers across the nation to develop new AIDS drugs and 19 centers to conduct clinical trials of promising AIDS drugs. The Institute has now expanded this program with 17 clinical study groups throughout the country.

NIAID scientists played a major role in developing a promising AIDS vaccine that entered safety and effectiveness trials at

Dr. Thomas Folks, senior investigator, NIAID Laboratory of Immunoregulation (left), with visiting medical fellow Dr. Guido Poli. Dr. Folks holds flask of cells for a test that reveals the presence of antibodies to the AIDS virus.

NIAID in August 1987. The Institute is also setting up cooperative groups of scientists around the country to develop other AIDS vaccines. As they are developed, these vaccines will be tested in six NIAID-supported Vaccine Evaluation Units across the United States.

With help from the Department of Energy, NIAID has established a computerized data bank to collect all the information about HIV in one place. And since 1983, NIAID has sponsored nearly two dozen conferences to present the latest AIDS information to physicians, nurses, and health care workers around the nation.

For the foreseeable future, AIDS is likely to remain a major health problem in the United States, especially for women. A growing proportion of them are infected with the virus through sexual contact with infected men, who presently outnumber infected women more than 9 to 1. Thus, women have many more opportunities than men of receiving HIV through heterosexual relationships. There is hope, however, that the aggressive anti-AIDS program mounted by NIH will soon develop vaccines, drugs, and treatments that can eliminate the danger for AIDS for women as well as for men and children. ■

"Until recently, the focus has been on male homosexuals, so women tended to take (the threat of AIDS) lightly. And they have not been taking steps to protect themselves."
Harold Ginzburg, M.D.

REPRODUCTIVE HEALTH

Infertility and Contraception

More than at any other time in history, women today have control over the timing of childbearing. Over the past 25 years, the freedom brought by the wide range of effective contraceptives has enabled women to pursue education and career without interruption, and to start families when they choose.

At the same time, however, the trend to delay childbirth may have contributed to another trend—an increase in the number of married couples who remain childless because of infertility.

At the National Institute of Child Health and Human Development (NICHD), research into infertility and contraception focuses on the basic biology of fertility, the mechanism of infertility and the control of fertility through contraception. In fact, the NICHD oversees the world's largest research program on reproductive issues. All of these efforts are aimed at helping couples have healthy children, and have them when they want them.

Infertility

The actual rate of infertility—inability to conceive after a year of trying—is difficult to assess. Certainly the number of visits to doctors for infertility has doubled in recent years. This may be because people are now aware that more can be done for infertility. But some experts suggest there is a true rise in infertility due to delayed childbearing, sexually transmitted diseases, and use of intrauterine devices (IUDs).

Whatever the reason, an estimated 11 percent of couples today are troubled by infertility. This includes those who have no children as well as those who have had at least one child but cannot have another. The good news is that advances in the diagnosis and treatment of infertility have improved the odds for success. Today 75 percent of infertile couples can be helped, up from about 50 percent two decades ago.

The first big step science took toward overcoming infertility was simply to understand the menstrual cycle, says Florence Haseltine, Ph.D., M.D., director of NICHD's Center for Population Research. "It wasn't even known until this century when a woman became pregnant," she said. "The ability to have children was considered a gift of the gods."

The concept of treating an infertile couple together has only been practiced widely since the early 1950s, Haseltine said. Previously, if a couple failed to get pregnant, it was thought to be the woman's fault. Today, some couples still do not realize that a modern fertility evaluation begins with the man.

For decades, researchers at NIH and around the country have worked to understand normal endocrine physiology—patterns in the rise and fall of reproductive hormone levels that enable women and men to reproduce. NICHD intramural scientists were among the first to develop sensitive tests, called radioimmunoassays, that can establish hormonal changes during the normal menstrual cycle. These tests measure blood levels of several reproductive hormones, including human chorionic gonadotropin (hCG), human luteinizing hormone, and human follicle stimulating hormone. The tests also helped scientists describe reproductive disorders such as the syndrome of "short luteal phase," a treatable form of infertility.

A few recent NICHD studies have focused on specific causes of infertility, such as the use of IUDs (particularly the Dalkon Shield and Lippes Loop). But more work has aimed at uncovering basic mechanisms of reproductive biology. Knowledge of the normal patterns of reproductive hormone levels, for instance, gives doctors a baseline for diagnosing certain forms of infertility caused by hormone disruptions. This knowledge has also guided development of drugs to induce ovulation and sperm production as well as the development of tests for detecting ovulation and pregnancy.

Tests that detect early pregnancy can help doctors treat infertility due to loss of a pregnancy very soon after conception; the woman may not even know she's been pregnant. In 1972, NICHD researchers developed the first specific blood test for the hormone hCG, which permitted detection of pregnancy within 10 days of conception. Previous tests needed six weeks of pregnancy to elapse before they were effective. In 1981, NICHD-funded

Research efforts of the National Institute of Child Health and Human Development (NICHD) are aimed at helping couples have healthy children when they want them.

scientists created an ultra-sensitive, highly specific test that has since been adapted for home pregnancy detection kits. The test kits are simple enough to use at home and give results in less than an hour, compared to a couple of days needed for previous tests.

Basic research that led to new treatments for reproductive disorders won a Nobel Prize for two NIH-supported researchers in 1977. Drs. Roger Guillemin and Andrew Schally, working independently, determined the structure of LHRH (luteinizing hormone-releasing hormone), a brain chemical that regulates reproductive processes. Since then, drugs based on LHRH have been developed to treat different forms of infertility in women and men. For example, LHRH is now being used experimentally to treat endometriosis, a leading cause of infertility in women. In a seeming paradox, some forms of the drug, administered in a particular way, can turn off the reproductive system. These are being developed and tested as contraceptives for women and men.

Contraception

Since the time of the pharaohs, women have been seeking better ways to avoid unwanted pregnancies. The most revolutionary technique discovered so far has been the use, beginning in the 1960s, of steroids taken by pill, implant, or injection.

"These things represent the development of the century in contraception," says Gabriel Bialy, Ph.D., chief of contraceptive development at the Center for Population Research. "For the first time women had something available to them that was highly effective, relatively safe and not coitally associated." They did not have to deal with it during sex.

The development of latex rubber in the mid 1800s marked the first really big advance in modern contraception, leading to the development of condoms, diaphragms and other devices that form barriers between egg and sperm. In the United States today, however, the most widely used form of birth control—albeit nonreversible—among married couples is sterilization: tubal ligation or, in men, vasectomy. Current research aims at finding ways to plug tubes now cut during sterilization so that it can be reversed by removing the plugs, Bialy said. This may be possible in five to 10 years.

None of the options available to the 29 million American women using birth control is totally effective, convenient, and reversible as well as free from side effects. Therefore, in addition to supporting the development of new methods of contraception, the NICHD funds studies to evaluate the effectiveness and safety of currently available contraceptives, including the pill, spermicides, sterilization, IUD's, and barrier devices, such as the sponge, diaphragm, and cervical cap.

Much of the Institute's effort has focused on oral contraceptives, the most popular form of reversible birth control. NICHD-sponsored research helped find, for example, that women who are smokers, over 35, or at risk for cardiovascular disease are more likely to develop serious complications, such as stroke or heart attack, when using the pill. On the plus side, other studies revealed that oral contraceptives also help protect women from pelvic inflammatory disease and cancer of the ovaries or endometrium.

Several current NICHD studies are looking at female sterilization, which some practitioners believe can cause menstrual abnormalities. However, no firm connection has yet been made between the two. Other projects are examining the relative safety and effectiveness of the most frequently performed sterilization operations in the United States.

In the 1970s the rate of tubal ligations rose dramatically to 63 percent of all sterilizations for contraception in 1977 from 28 percent in 1971, partly because animal studies raised concern over the safety of vasectomy. In response, the NICHD investigated vasectomy in nearly 40,000 men. This study found vasectomy to be safe. Since that research was publicized, the rate of female sterilization has stopped climbing and has fluctuated around that point.

In the area of barrier devices, the Institute has investigated the effectiveness, acceptability, and safety of the sponge. And, in a multicenter clinical trial, the NICHD found that a new device called the cervical cap is as effective as the diaphragm. The data has led to the recent approval of the cervical cap. Further NICHD studies on barrier devices, on brain hormones that control reproduction, and on biodegradable implants for contraceptive hormones aim to give women more and safer birth control options.

"In almost every area of fertility regulation, I think you will see advances. . . . There will be no fantastic changes," Bialy said, "but more variety. . . . We all have our own individual preferences." ■

Oral contraceptives represent a tremendous advance in preventing unwanted pregnancies. The National Institute of Child Health and Human Development (NICHD) has funded numerous studies investigating the safety and effectiveness of the pill, the most popular form of reversible birth control.

Healthier Mothers and Babies

Over the past 50 years, medical science has greatly increased the chances of an infant and its mother's surviving the trauma of pregnancy and childbirth. Big improvements have evolved out of many small advances in prenatal research, medical technology, and public education rather than from isolated, spectacular breakthroughs. And the cumulative effect has been dramatic.

"If you look at the numbers, you look at a fantastic improvement over the past few decades," said Sumner Yaffe, MD, director of the Center for Research for Mothers and Children at the National Institute of Child Health and Human Development (NICHD).

The infant mortality rate has dropped more than 80 percent in the past half century, to an estimated 10.6 deaths per 1,000 live births in 1985. There were 60.1 per 1,000 in 1934. But the biggest improvement has come in the maternal death rate, which fell almost 98 percent over nearly the same time. In 1984 it had fallen to an estimated 7.8 deaths per 100,000 live births from 376 per 100,000 in 1940. The huge decline in maternal deaths came primarily from the use of antibiotics developed in the 1940s and '50s.

"If you go back 100 years, infection was always the reason for the mortality of mothers in childbirth," Yaffe said. But since the advent of antibiotics, "mothers don't die any more."

In addition, public education about good nutrition has led to healthier mothers better able to survive childbirth. They have also benefited from the development of better prenatal care programs that detect health problems early and from better techniques for managing high risk pregnancy conditions such as hypertension, diabetes, and hemorrhage. And the development of the birth-control pill has allowed women to have fewer pregnancies and to space them further apart. Consequently, today's mothers are better able than their mothers to recover physically and psychologically from each pregnancy.

For an infant born in the United States today, the most advanced neonatal care techniques in the world have been developed. Many of them involve watching for fetal problems during pregnancy and labor. The early diagnosis allows a doctor to treat some problems during pregnancy and to prepare for others when the child is born.

"There's no question that the care of the small infant has improved fantastically," Yaffe said. "If you produce a 2-pound baby, we're No. 1 in the world for taking care of it."

Black mothers and babies encounter more difficulties in pregnancy than other groups. For instance, the infant mortality rate is higher among blacks. Researchers supported by the NICHD are looking at factors that may affect the outcome of pregnancy in black women, such as lifestyle and eating habits, to see what can be done to improve the likelihood of healthier babies.

Scientists supported by the NICHD were among the first to show that the fetal heart rate can be monitored electronically during labor, allowing doctors to take protective measures if the baby is in trouble. The development of diagnostic ultrasound—in which the echo of sound waves emitted to the mother's abdomen forms an image of the infant on a screen—now allows technicians to identify twins, placental problems, or other pregnancy complications much earlier than before. They can also examine the fetus' anatomy and physiology, and can monitor its growth.

The death of President John Kennedy's two-day-old son from respiratory distress syndrome, or RDS, in 1963 focused national attention on the problem of RDS in babies. It speeded the effort at NICHD—founded only the year before—to find an effective treatment for the disorder. The Institute supported development of tests to evaluate fetal lung maturity, of hormones given to the mother to hasten fetal lung development, and of a procedure to ventilate the infant's lungs. Researchers are also experimenting with an aerosol technique for introducing to the lungs a substance called surfactant. Surfactant lines the tiny air sacs, or alveoli, of the lungs and is necessary for exchanging oxygen. However, premature babies often do not produce enough of the substance. Administering surfactant at birth prevents RDS from developing in many premature infants, and if it does develop, it is usually a much milder case than otherwise would have been expected. These advances have greatly improved the survival chances of the 40,000 premature and low-birthweight newborns who develop RDS every year.

Low birth weight, though, continues to be a problem and contributes significantly to infant death in the United States. The infant mortality rate here is higher than in a dozen other western countries, Yaffe

Due to advances in research, technology, and education, more mothers and babies are surviving pregnancy and childbirth than ever before.

"There's no question that the care of the small infant has improved dramatically."
Sumner Yaffe, M.D.

said. And among American cities, it is highest in the nation's capital. Most of the factors contributing to low birth weight are non-medical, socioeconomic problems, such as alcoholism, drug abuse, poor nutrition, infection, lack of access to medical care, and smoking. "If women would just stop smoking," Yaffe said, "we'd make significant progress."

Significant progress has been made in another important area of infant care, that of treating Rh disease, or erythroblastosis fetalis. With NIH support, a treatment was developed that has virtually eliminated this disorder, which as recently as 1960 killed an estimated 5,000 to 6,000 infants.

Rh disease can occur when a woman with an Rh-negative blood type becomes pregnant by a man with Rh-positive blood. The fetus' blood circulates through the placenta to the mother. There, if the fetus is Rh-positive, the mother's immune system produces antibodies to fight the Rh factor as they would fight an invading foreign substance. These antibodies can leak back across the placenta and start to destroy blood cells in the fetus. The result is serious anemia, jaundice, or even death.

In 1963, a team of NIH-supported investigators developed a treatment, given to the mother, that coats the Rh factor when it comes from the fetus. The coating, in effect, hides the Rh factor from the mother's immune system so that it does not produce antibodies that might cause the disease in this or future infants. It is advances such as this one—supported by the NIH—that have led to a better and healthier outcome for mothers and their babies. ■

Preventing Birth Defects

Fifty or 100 years ago the prospect of giving birth to a defective infant was a big worry to couples expecting a baby. Today, the problem is still big: more than 250,000 babies are born with birth defects in the United States each year. But progress in understanding birth defects and advances in dealing with them have given potential parents the knowledge to minimize the risks of birth defects, cope successfully with the ones that do occur or avoid them altogether.

"The biggest area of advancement is in diagnosis," said Joel Schindler, Ph.D., health scientist administrator in the Genetics and Teratology (study of birth defects) Branch of the National Institute of Child Health and Human Development (NICHD). The advance is reflected in the downward trend in the number of children born with certain defects, such as Down syndrome. "It's a direct result of being able to identify the genetic abnormality and of genetic counseling."

The great leap forward in diagnosis came in the late 1960s and early 1970s, when the ability to grow cells *in vitro* led to the development of amniocentesis. This involves extracting a small amount of amniotic fluid from the mother's womb during the 15th to 18th week of pregnancy, growing the cells in a lab and analyzing them for defects. Amniocentesis allows scientists to identify hundreds of genetic abnormalities in the fetus, including Duchenne muscular dystrophy, Down syndrome, Tay-Sachs disease and other conditions that can lead to severe physical handicaps or mental retardation.

More recently, chorion villus sampling (CVS) has been developed, in which microscopic cells from the embryo's outer membrane, or chorion, are extracted in the eighth to 10th week of pregnancy and examined for genetic abnormalities. Knowledge gained by CVS, which is still experimental, or by amniocentesis provides valuable information to doctors and parents in helping them prepare for the problem.

"We are not in a position to repair a bad gene," Schindler said, adding that this might be possible by the year 2000. But "if you know there's a medical problem, then you can deal with it."

For instance, the development of a simple blood test has made it possible to screen newborns for phenylketonuria (PKU), an enzyme deficiency that affects one in 15,000 babies. If left untreated, it causes severe mental retardation. It can be controlled in childhood by a diet low in phenylalanine, a protein found in foods such as meat and cow's milk. NICHD studies are trying to determine whether, when PKU girls grow up, putting them on a special diet prior to or during pregnancy can prevent a second PKU generation.

As the techniques for identifying genetic abnormalities and chromosomal defects has progressed, the ability to predict and, in some cases, to treat birth defects has increased as well. Explaining all this to potential parents has grown into a science of its own called genetic counseling.

"Genetic counseling is a communication process which deals with the human problems associated with the occurrence or the risk of occurrence of a genetic disorder in a family," said Felix de la Cruz, special assistant for pediatrics in the Mental Retardation and Developmental Disabilities Branch of NICHD.

"My gut feeling is that genetic counseling has reduced the incidence of live births with birth defects," de la Cruz said. "There are a number of options" open to people at risk of having an abnormal child. They could, for instance, get a sperm or ovum donation to bypass a probable gene defect. Or, knowing the medical advances in treating defects, the couple might decide they can cope with an abnormal child if they had one. Or they might choose to avoid having children altogether.

There is now a growing number of doctors, psychologists, nurses, and social workers certified as genetic counselors by the American Board of Human Genetics. They help would-be parents make more informed decisions by explaining the medical facts of their case, the role of heredity and their options, as well as by helping them choose the best course of action and adjust to the outcome. ■

In this country, more than 1 million teenage girls become pregnant each year.

Teen Pregnancies

Teenage pregnancy remains a major problem in the United States today despite a declining birth rate among American adolescents over the past 10 years. There are still too many unwanted pregnancies, too many births among younger teens and too many infants born to adolescent mothers unable to adequately care for them.

Compared with levels in other developed nations, teenage pregnancy, abortion, and childbearing in the United States have remained remarkably high since 1970. American girls under age 15 are at least five times more likely to give birth than young adolescents in any other developed country. In fact, more than 1 million teenage girls in the United States become pregnant each year, according to a 1986 report by the National Academy of Sciences. Just over 400,000 have abortions and nearly 470,000 give birth.

"Sexual activity rates (among teens) are just as high in Europe, but their birth rates are lower," said Sandra Hofferth, Ph.D., health scientist administrator with the National Institute of Child Health and Human Development (NICHD). "It's not that they are having more abortions. There are fewer pregnancies."

Changing patterns of behavior among American adolescents aggravate the problem of teenage pregnancy. The proportion of sexually active teenage girls has increased 66 percent since the early 1970s. The time they are sexually active outside wedlock has also grown at both ends. Women today marry at about 23.3 years of age, nearly a year and a half later than they did at the turn of the century. And they mature sexually at about 12.8 years of age, more than eight months earlier than their grandmothers in 1900.

From this period of unmarried sexual activity comes an increasing number of young mothers faced with raising their child without help from a husband. The majority of teen mothers today are unmarried, and nearly half of these are 17 or under. Many became pregnant very soon after starting sexual activity.

"The risk (of pregnancy) is very high during the six months after first intercourse," Hofferth explained. "Most people are sexually active for about a year before they go to a clinic or doctor for contraceptives."

The primary danger of early pregnancy is to the fetus. Young teens are highly unlikely to receive good nutrition and prenatal care, Hofferth said. They are apt to have pregnancy complications and bear small infants suffering medical problems associated with low birth weight.

In addition, research supported by NICHD and others consistently shows that children born to teen mothers are disadvantaged compared with children born to older mothers. Small differences in I.Q., achievement and social and emotional development persist as the children grow older and appear to intensify during elementary school and teen years. They also have more behavior problems, such as running away, fighting, stealing, and smoking.

The National Center for Nursing Research (NCNR), established at NIH in 1986, is funding research that focuses not only on the impact of teenage pregnancy on mothers and children but also on promoting the adolescents' general and reproductive health. One such study examines adolescent health-compromising behavior, including sexual intercourse, drug abuse, and overeating as well as factors that may lead to and support these practices. With this information, researchers hope to develop ways to change this behavior.

Other NCNR-supported projects are investigating the development of self-concept in adolescent mothers and its relationship to successful mothering; how adolescents cope with pregnancy through the first year of motherhood; and the importance of mother-child interaction to the mental and physical health of the child.

At NICHD, the research emphasis is on prevention. "The most important method of reducing pregnancy and births among teens is contraceptives," Hofferth said. "Data show that teenagers can use contraceptives and can use them well."

A survey has shown that the proportion of teenagers who always use contraceptives or used them at first intercourse rose to 48 percent in 1982, up from 38 percent six years earlier. The proportion of teens reporting that they never use contraceptives dropped sharply to 15 percent over the same period, down from 36 percent. Pregnancy rates among sexually active teens have, in fact, dropped over the past 4 years.

Several NICHD studies are trying to find out which teenagers are using contraceptives and why. Researchers also want to know how teens obtain contraceptives and how effective the devices are. The information will be used to develop more effective sex education programs for teens.

"We hope to have a better idea of how to get teens to use contraceptives," Hofferth said, "because we think that's the best way of preventing teenage pregnancy and its consequences." ■

Many women with careers outside the home choose to postpone motherhood. Current studies are showing that older women in good health who receive prenatal care may not face as many risks as once believed.

Late Pregnancies

Since the early 1960s, the increasing desire to have careers outside the home has prompted many women to postpone motherhood, and the introduction of oral contraceptives has made this possible. As a result, the proportion of women having their first child after age 30 has more than doubled, to 12.9 percent of all first births in 1984 compared with just 5.3 percent in 1965.

From a socioeconomic standpoint, delayed childbearing appears much more advantageous. Studies supported by the National Institute of Child Health and Human Development (NICHD) have found that older mothers tend to have more education, higher status jobs, and better incomes than do mothers five or 10 years younger. They also are more likely to have higher aspirations for their children and more money to provide material goods and a good education.

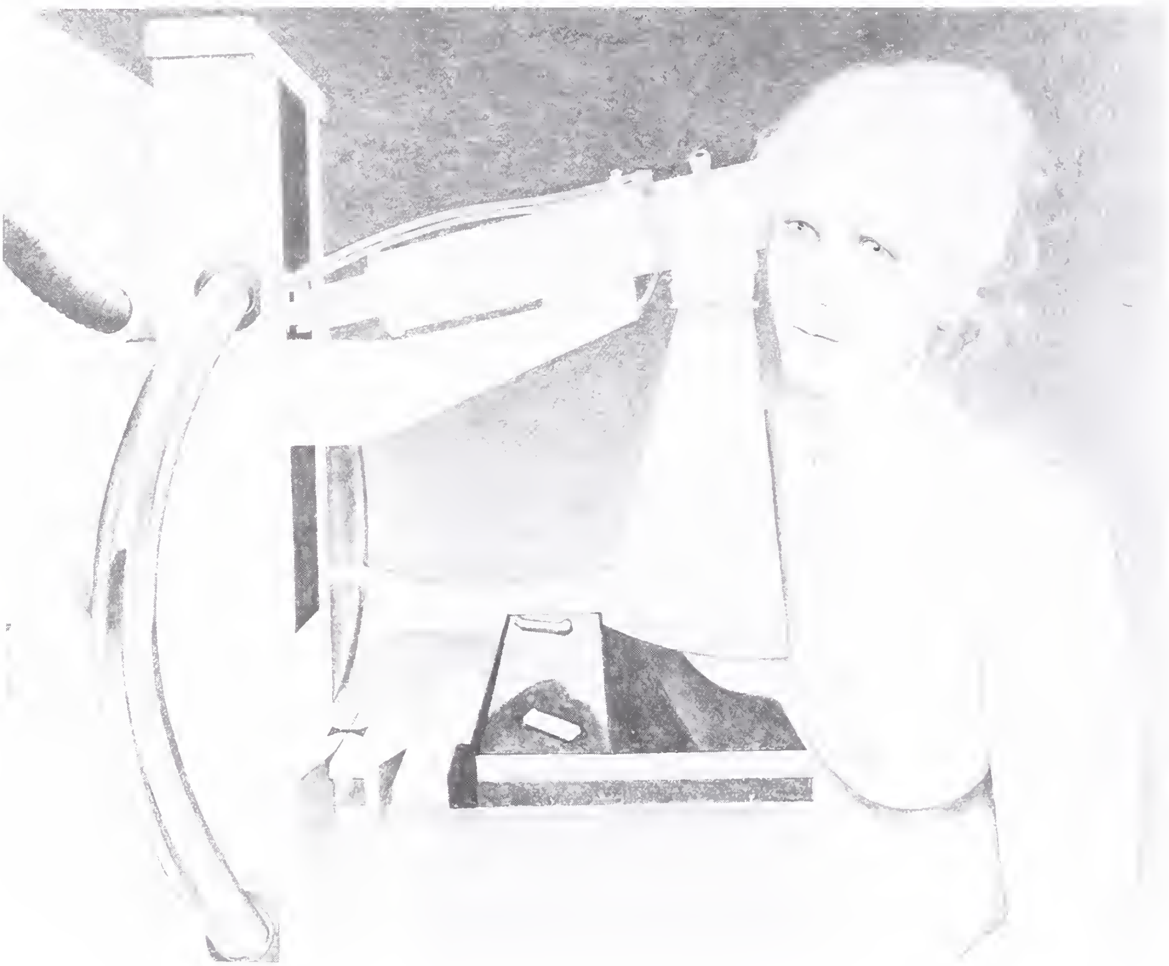
In addition, studies show that women over 30 at the birth of their first child are better off economically when they reach age 60 than women who start their families at a younger age. The older mothers prefer generally to keep their families small and to space pregnancies further apart. And almost half of those who worked prior to childbirth return to work within a year.

From a genetic viewpoint, women do face two risks that increase with age. The closer they get to 40 the more likely they are to have a child with Down syndrome, the most common genetic cause of mental retardation. And they face a greater chance of multiple births. Women age 35 to 39 were found to be twice as likely to have twins with their first pregnancy as were teenagers, even if they had not taken fertility drugs.

From a medical point of view, new studies are challenging the longheld belief that older women have more pregnancy complications than younger women do. Recent studies suggest that today, as long as they are healthy and receive good prenatal care, women run no greater risk of birth problems in their 30s than they do in their 20s or late teens.

"There is data to suggest that the rates (of successful birth) are about the same," said Donald McNellis, M.D., special assistant for obstetrics in NICHD's Perinatology Branch. Although more research is needed to document this finding, McNellis said "there doesn't seem to be more risk based solely on age." ■

Breast Cancer



Woman Having Mammography

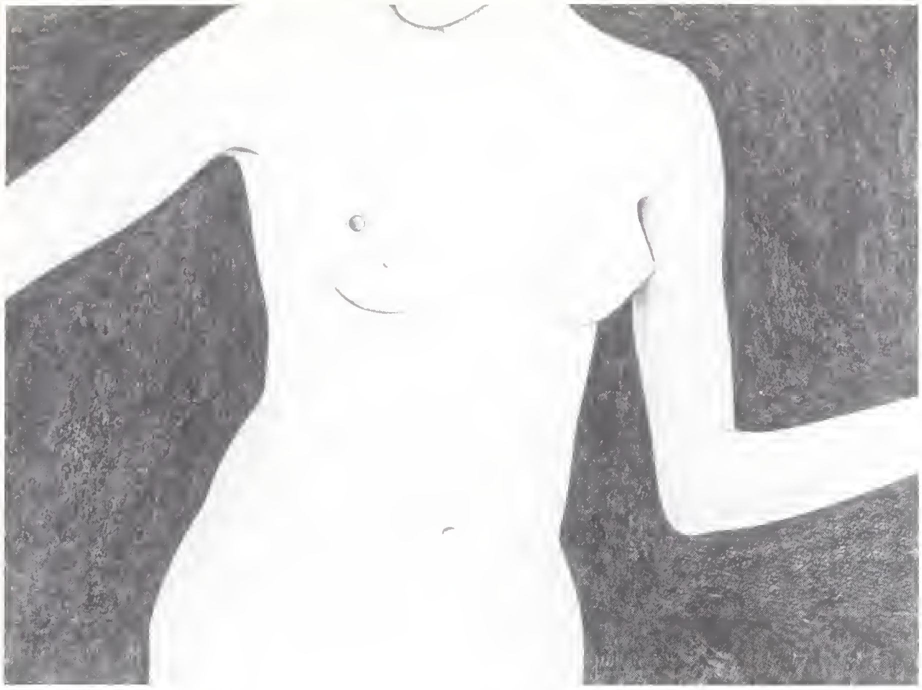
Graphic courtesy of the NCI Breast Cancer Materials. Artist-Donald Gates

"Women and the health professionals who care for them have yet to take full advantage of the opportunities for breast cancer screening," said Charles Smart, M.D., of the National Cancer Institute (NCI). "Great potential exists to improve early detection of breast cancer through physical breast examination and mammography."

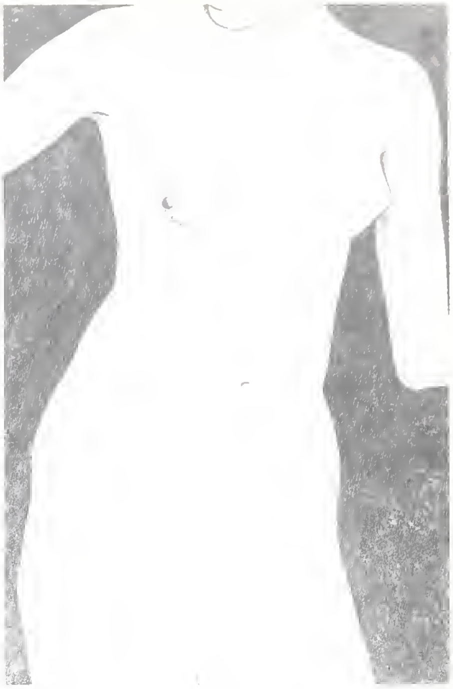
Today more treatment options are available, particularly when breast cancer is detected early. The surgery is less disfiguring and debilitating, and reconstructive surgery is available. And more women are alive today who have a history of breast cancer. Early detection and improved treatment have boosted the five-year relative survival rate for breast cancer, all stages, to 74 percent, up from 63 percent two decades ago. If detected and treated at an early stage when cancer is confined to the breast, the five-year relative survival rate is now 96 percent, but if cancer cells have spread to other areas of the body, the rate drops.

"Research suggests that only one out of five women age 50 or more have ever had a mammogram and even fewer have regular examinations," said Dr. Smart, chief of NCI's Community Oncology and Rehabilitation Branch. "Many balk at the idea of receiving radiation, an unwarranted concern at such a low dose, or because of the cost of mammography, which ranges from $35 to $200. Also, many doctors do not recommend a periodic mammogram for women with no cancer symptoms, thinking the expense, time, and radiation exposure outweigh the benefit of early detection in a few."

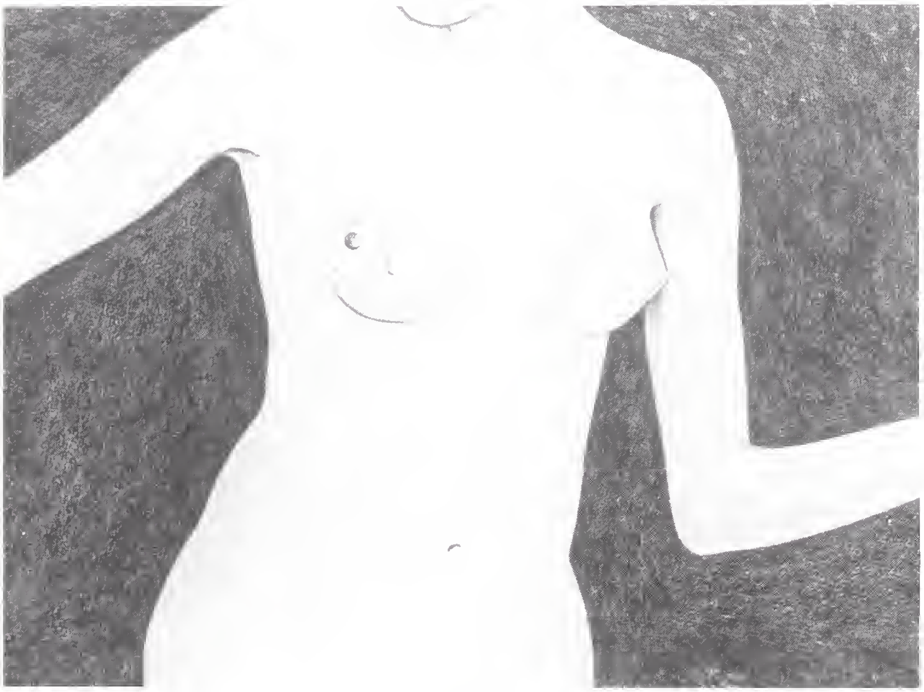
But, Dr. Smart said, "We could reduce mortality from breast cancer 30 to 40 percent in women 40 and above if



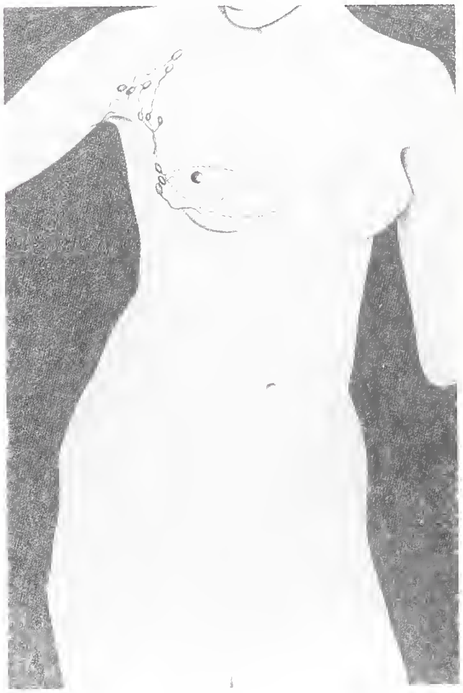
Lumpectomy



Partial or Segmental Mastectomy



Total Mastectomy



Modified Radical Mastectomy

Surgical Options for Treating Breast Cancer

These graphics depict the surgical options available to women for the treatment of breast cancer. Each type of breast surgery has advantages and disadvantages and sometimes are used in conjunction with other types of treatment. The decision to select an appropriate surgery is based on a number of factors that a woman should discuss with her doctor.

Graphics courtesy of the National Cancer Institute, the Breast Cancer Digest

asymptomatic (those without symptoms) women would get routine physical breast exams and mammograms."

Assuming current rates of breast cancer continue, one in about every 10 women in the United States will develop breast cancer during her lifetime. In 1987, an estimated 130,000 women were diagnosed with breast cancer and 41,000 died of it.

About 45 percent of women aged 50–70 now get annual physical breast examinations and about 15 percent get annual mammograms. Estimates of the percentage of women who perform monthly breast self examination vary from about 20 to 40 percent. Studies show most breast cancers are found by women themselves either accidentally or by self examination. According to a recent study by University of Southern California scientists, however, many women do not perform self breast examination correctly.

NCI's guidelines for early detection of breast cancer are that every women perform monthly breast self examination and have an annual physical examination by a physician. Mammography should be considered for women age 40–49 every one or two years and for all women age 50 or more annually. Women who have had breast cancer at any age need an annual mammogram. A baseline mammogram is not among NCI's guidelines, but various medical organizations have different recommendations for mammography. NCI is now working with national medical groups to develop more uniform guidelines.

In 1987, the Institute funded a four-year effort to promote and sustain the routine use of mammograms and clinical breast exams for women age 50 and over in a variety of communities around the country. The study aims to persuade women to have regular screenings, to encourage doctors to recommend them, and to guarantee that radiologists develop the capacity to improve image quality while using minimal radiation.

Treatment for breast cancer, which involves surgery 93 percent of the time, has become much less extensive since the 1950s. The standard treatment was once the Halsted radical mastectomy, introduced about 1890. It was a disfiguring and debilitating procedure that removed not only the breast, but also the underlying chest muscles and under arm lymph nodes. In the 1950s, doctors learned they could often treat breast cancer just as effectively with more limited surgery.

As recently as 1985, a major NCI-funded clinical trial on breast cancer treatment showed that lumpectomy followed by radiation is as effective as removal of the entire breast for many women with early stage disease. This finding has meant that an increasing number of women now have the option to have less disfiguring surgery.

For many years, NCI has explored the use of hormones and chemotherapy after primary treatment to reduce the risk of cancer recurrence from wandering cancer cells that escaped from the original tumor before it was removed. For example, tamoxifen, an antiestrogen drug, has been shown to reduce the chance of recurrence and extend disease-free survival in postmenopausal patients whose cancer cells need estrogen to grow. This treatment can reduce by 20 percent the number of postmenopausal patients who suffer recurrence and death. In premenopausal patients, combination chemotherapy has been shown to reduce death by 25 percent and increase disease-free survival significantly. Also, the National Center for Nursing Research is supporting a study to determine whether aerobic exercise can prevent physical and psychological deterioration in such patients while they receive chemotherapy.

Chemotherapy and hormones offer better prospects as well for women whose cancer has already spread to distant organs and tissues. Nearly 50 percent have a response to combination chemotherapy and a third benefit from hormone therapy. Recent studies sponsored by the NCI suggest that chemotherapy and hormones can be combined to produce higher remission and longer survival rates. Researchers also hope that developing technologies—such as monoclonal antibodies, gene splicing, and biological response modifiers—will help control advanced disease.

Studies by NCI and other research centers have helped to identify factors, such as age and a family history of breast cancer, that carry varying degrees of risk for breast cancer. No one factor or combination of factors has been found, however, that can predict the occurrence of breast cancer in any one individual. Some studies suggest that a high-fat diet, like the American diet where 40 percent of daily calories are fat, may increase risk for breast and other cancers. NCI is presently studying the fat and breast cancer question. Because of the evidence linking diet and cancer, NCI encourages Americans to change their eating habits and adopt a more healthful low-fat, high fiber diet that may reduce their risk for cancer.

For information on breast cancer including breast self examination instructions, mammography, treatment, and diet and cancer, write NCI's Office of Cancer Communications, Bldg. 31, Room 10A24, Bethesda, MD. 20892; or call toll-free the Cancer Information Service at 1-800-4-CANCER. ■

Cervical Cancer

Thanks to the Pap test, American women have a very effective way of protecting themselves against cancer of the cervix. For the past three decades, the occurrence of new cases on invasive cervical cancer and deaths from the cancer have been declining steadily in the United States. But more women need to take advantage of this life-saving test.

"It is almost universally agreed that the Pap smear has had a tremendous influence in reducing the mortality of the disease," said Philip Prorok, Ph.D., chief of the National Cancer Institute's (NCI) Cancer Screening Section. "The incidence and mortality rates have been coming down for some time. Many people would attribute much of that to screening programs and the Pap smear."

Developed by and named after American Dr. George Papanicolaou in 1928, the Pap smear entered into wide use in the 1950s.

The NCI played a major role in demonstrating that such a test could be used in large groups to detect cancer. Through the establishment of massive demonstration projects—first at Memphis in 1953 and then at Louisville in 1956—the Institute showed the feasibility and effectiveness of large-scale screening for the disease. Although death from invasive cervical cancer had begun to decline before the 1950s due to improved surgical techniques, the continuing drop in incidence and mortality rates since then is generally attributed to the Pap test.

The Pap test, or Pap smear, is a simple, painless test in which cells are collected from the surface of the cervix and examined under a microscope. If abnormal cells are detected, further tests are done to establish or rule out the presence of dysplasia—abnormal cells that are not cancerous but may go on to develop into cancer, early cervical cancer, or invasive cervical cancer.

Development of the Disease

The development of cervical cancer often starts with dysplasia. In some women, dyplasia goes through a series of changes and then develops into cancer if it is not treated. Very early cancer, or carcinoma *in situ,* involves only the top layer of cervical cells and does not invade the deeper layers of cervical tissue for many months, perhaps years. Very early cancer is curable in almost 100 percent of cases if treatment is started at the time of diagnosis.

If left untreated, it may advance to invasive cancer, which is cancer that has spread deeper into the cervix and/or to nearby tissues or organs. The sooner invasive cancer is diagnosed and treated, the better the chances for cure. The 5-year relative survival rate (the percentage of patients who survive 5 years after a diagnosis of cancer, adjusting for normal life expectancy) for women with early-stage invasive disease is 80 to 86 percent. But once the cancer spreads to distant organs, the rate plummets to about 32 to 40 percent.

Although the cause of cervical cancer is uncertain, women who began having sexual intercourse before age 18 and women who have had many sex partners have an increased risk of developing the disease. Scientists also know that the cancer occurs most often in women of low socioeconomic groups.

Scientists have suspected for some time that viruses are involved in development of the cancer. There is growing evidence suggesting that viruses called papillomaviruses may play a part both in the development of dysplasia and in the change from dysplasia into cancer. Some papillomaviruses cause genital warts, which may appear before dysplasia. Most scientists believe that several steps are needed for dysplasia to change into cancer, and some now believe that papillomaviruses may start the process. Research on these viruses is now under way at NCI and at other research centers.

Early Detection

The key to controlling cervical cancer is detecting it as early as possible. NCI recommends that all women who are, or have been sexually active, or have reached age 18 years, have an annual Pap test and pelvic examination. After a woman has had three or more consecutive satisfactory normal annual exams, the Pap test may be performed less frequently at the discretion of her physician.

Unfortunately, many women are not taking advantage of the Pap smear. This year, invasive cervical cancer will be diagnosed in about 13,000 American women and will kill nearly 4,500.

The National Cancer Institute encourages women to take greater advantage of this life-saving cancer screening test. Presently, 79 percent of women age 20 to 39 have Pap tests every three years and 57 percent of women aged 40 to 70.

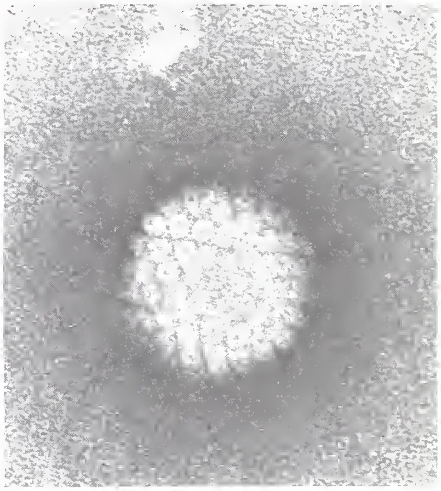
The majority of American women are aware that Pap smears can find early, curable cancer of the cervix. A 1986 survey conducted by the Gallup Organization for the American Cancer Society showed that 92 percent of white women were aware of the Pap test and 85 percent had had the test at some time. Only 76 percent of black women knew of the test and 70 percent had had it.

Certain Women at Greater Risk

In black women, the occurrence of new cases of cervical cancer is almost 2½ times higher than among whites, and the death rate is almost three times higher.

"There are some subgroups of our population that don't come into contact with the medical care system where women tend to get these screenings," Dr. Prorok said. "It may be that they don't want to or they can't get the screening."

Today NCI is funding studies in the black population to identify barriers to controlling cervical cancer. In addition, NCI is supporting a wide variety of other research on prevention and treatment. Through this research and efforts to encourage wider use of the Pap smear, incidence and mortality rates for cervical cancer may continue to drop much further. ■



Electron micrograph of the papilloma virus which occurs in human warts. Warts on the hands and feet have never been known to progress to cancer, however, cervical warts can go on after many years to become cancerous.

Lung Cancer

Lung cancer is one of the most serious threats to women's health today. In 1987, the disease caused the deaths of an estimated 44,000 women in the United States. When the final statistics are available, it is projected that this year lung cancer will surpass breast cancer as the leading cause of cancer deaths among women. It is a leading killer among all cancers, which together claim the lives of more American women than any other cause except heart disease.

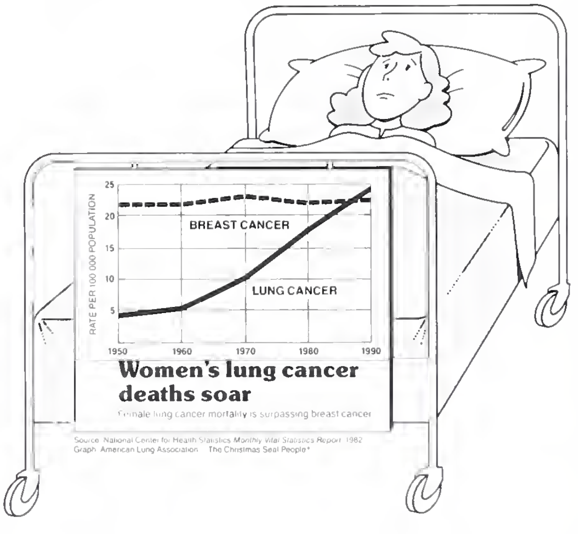
Over the past 35 years, lung cancer rates among women have increased an alarming 250 percent, and unless current trends change, these rates may more than double by the year 2000. And the rate is expected to continue climbing past the year 2000 due to the explosion in the number of women smoking in the 1960s and '70s.

"Lung cancer is an extremely serious problem that has just skyrocketed," said Margaret Mattson, Ph.D., project officer for the Women in Smoking project of the National Cancer Institute's (NCI) Smoking, Tobacco and Cancer Program. "We think that the rates will continue to go up in the next 10 to 15 years."

Lung cancer is particularly difficult to diagnose early and to treat. In about 50 percent of patients, lung cancer has already spread to other parts of the body by the time it is discovered. Only 16 percent of women who get lung cancer are still alive five years after diagnosis. NCI conducts and funds basic research on the mechanisms by which lung cancer develops, spreads, and resists treatment as well as on methods of earlier detection and diagnosis.

Smoking the Major Cause

The No. 1 cause of lung cancer in women is smoking. In fact, more than three out of four women who die from lung cancer are smokers. The habit can also lead to other life-threatening diseases such as coronary heart disease, chronic obstructive pulmonary disease, and other cancers. Said Mattson, "About one third of smokers will die as a direct result of their smoking."



Graphic courtesy of the American Lung Association

At the turn of the century, the death rate and number of cases of lung cancer were low for both women and men. During the 1930s, however, these figures for men jumped sharply due to the large numbers of men who earlier had switched to cigarettes from other forms of tobacco. At that time, it was socially unacceptable for women to smoke. But with the social changes brought by World War II, more women began the habit. The percentage of women smokers continued to rise through the 1960s, peaking in 1965 at 34 percent. Today more than two decades later, 27.9 percent—nearly one of every three adult women—still smoke. Women are quitting the habit but not at as fast a pace as men.

Another disheartening statistic is that about 20 percent of high school senior girls reported in 1986 that they smoked cigarettes daily. In comparison, 17 percent of high school senior boys smoke.

> **"The best approach to fighting lung cancer is not to smoke . . ."**
> Margaret Mattson, Ph.D.

The Good News—It's Preventable

However, there is good news. Lung cancer is the most preventable cancer. In most cases women can prevent this disease if they avoid using tobacco in any form. "The best approach to fighting lung cancer is not to smoke," Dr. Mattson said. "The second best approach is that if you are a smoker, quit smoking."

NCI is focusing part of its research toward persuading specific groups not to smoke or to quit if they have already started, specifically to women. One study is exploring the role of social support in helping women to stop smoking. Another focuses on the fear of gaining weight, which keeps some women and men from quitting. A third study involves public health maternal clinics, where researchers hope to persuade women to stop smoking for their health and the health of their unborn. A fourth aims at helping nurses to quit smoking and teaching them to teach others how to stop.

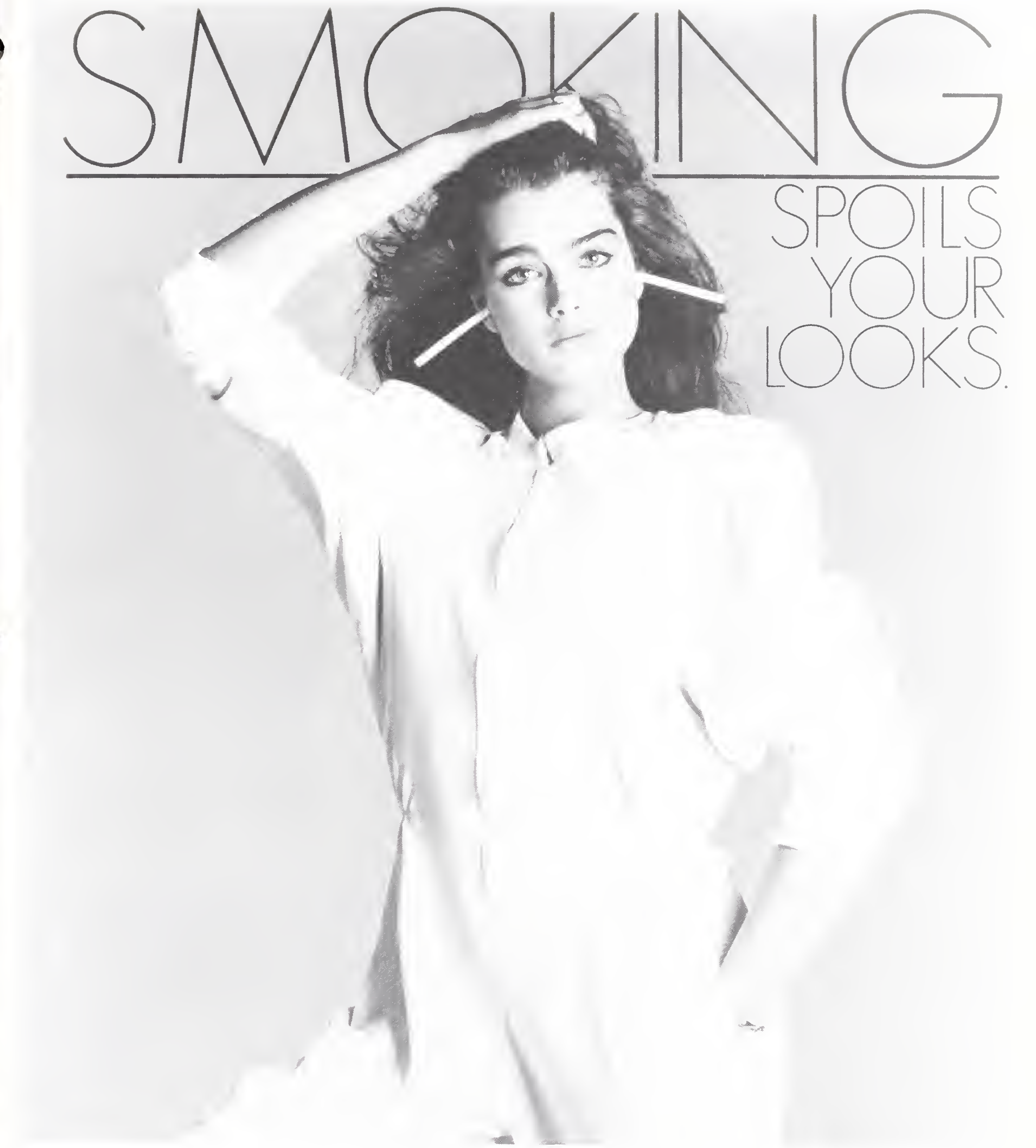
"The goal is to take information gained from these studies and make it widely available as soon as possible," Dr. Mattson said, "so that programs can be developed across the country to help women stop smoking."

NCI has set a goal to reduce the overall U.S. cancer death rate 50 percent by the year 2000. One objective is to reduce the percentage of adults who smoke from 34 percent to 15 percent or less by 1990, and to reduce the percentage of youths who smoke by age 20 from 36 percent to 15 percent or less.

Efforts to discourage smoking are paying off. The percentage of women who smoke has slowly been dropping since 1965 while the percentage of former smokers has grown. And today the proportion of young women who have never smoked at all is on the rise.

Where to Get Information

For information on lung cancer or for the free booklet "Clearing the Air: How to Quit Smoking . . . and Quit for Keeps," write NCI's Office of Cancer Communications, Building 31, Room 10A24, Bethesda, MD 20892; or telephone the Cancer Information Service, 1-800-4-CANCER. ■



THERE'S NOTHING ATTRACTIVE ABOUT SMOKING . . . As illustrated in this poster by Brooke Shields, top model, actress, and former National Youth Ambassador for the American Lung Association. The campaign, conducted in 1981, challenged the idea that smoking is glamorous.

Photo courtesy of the American Lung Association

CARDIOVASCULAR DISEASES

Cardiovascular Diseases

In 1908, heart disease replaced infectious diseases as the leading cause of death in American women. And, except during the influenza epidemic of 1918–1920, it has held that position ever since. The declining death rate for infectious diseases also cleared the way for stroke to move into third position, behind second-ranked cancer.

Today the fatality rates of both these cardiovascular diseases are declining in the United States. The death rate from heart disease dropped nearly 40 percent from 1963 to 1983 while the rate for stroke fell almost 60 percent. But they and other cardiovascular disorders still present a major problem for women's health.

"The decline (in cardiovascular diseases) seems to be slowing, especially for women," said Elaine Eaker, Sc.D., an epidemiologist with the Epidemiology and Clinical Applications Division of the National Heart, Lung, and Blood Institute. "Heart disease is still the No. 1 killer of women (and) stroke is the third leading killer."

Cardiovascular diseases are disorders of the heart and blood vessel system. They generally begin with atherosclerosis, a condition where artery walls grow thick and stiff and become plated inside with fatty deposits. The process slowly reduces the flow of blood and leads to a variety of cardiovascular problems.

Atherosclerosis of the coronary arteries, which feed blood to the heart muscle, is called coronary heart disease. CHD sometimes produces severe chest pains, or angina pectoris. If a clot lodges in a narrowed coronary artery, blood stops flowing to that part of the heart. The muscle begins to die and the person has a heart attack. The development of CHD, heart attack and its consequences is generally called heart disease. If a clot lodges in a narrowed artery leading to the brain, the person has a stroke and may suffer brain damage.

In women, the magnitude of heart disease has only recently been recognized. Together, cardiovascular diseases cause 51 percent of the deaths in American women: 26 percent are due to heart disease, 10 percent to stroke and 15 percent to other cardiovascular disorders. Death rates for these are higher for black women than for whites. In addition, about 1.2 million women suffer from heart disease, 1.6 million have hardening of the arteries, 5.6 million have varicose veins—four times more than the number for men—and 25 million have a serious problem with hypertension, or high blood pressure.

Less is known about the cause, prevention, diagnosis, treatment and course of cardiovascular disease in women than in men. Research in the past has focused on men, who at a young age have more frequent and severe CHD than women and at middle age have three to four times more heart attacks. Women were not represented as frequently as men in some studies on risk factors and treatment of coronary heart disease.

"Women should be included in more studies," Eaker said, "We need to know a lot more about what's going on in them."

Scientists are still trying to unravel the many, complicated causes of cardiovascular diseases. Research into coronary heart disease has uncovered several factors that seem to put women and men at higher risk for CHD as well as for cardiovascular diseases in general. Risk factors include cigarette smoking, high blood cholesterol level, obesity, diabetes mellitus, and high blood pressure. About 27 percent of women have mild or severe hypertension or are on anti-hypertensive drugs, 7 percent of women over 45 have diabetes and an estimated 37 percent of women are overweight. High blood cholesterol, high blood pressure, and cigarette smoking are the most telling risk factors.

About 25 million American women smoke cigarettes, and the number is increasing. Women under age 23 are the fastest growing group of smokers. Among teenagers, the proportion who smoke is higher among girls than boys. And women who smoke are smoking more cigarettes. Thus, the rates of coronary heart disease are likely to increase disproportionately in women as more of those who smoke reach the age where symptoms start to occur.

High levels of cholesterol in the blood have been shown to promote development of atherosclerosis. One out of five women has more than enough cholesterol in the blood to put her at risk for this and other cardiovascular diseases. Elderly women generally have higher average blood cholesterol levels than elderly men. Below 50, though, women have slightly lower average levels. Levels of HDL-cholesterol, the so-called "good" cholesterol that protects against heart disease, are higher in women than men at all ages.

In addition, several risk factors for cardiovascular diseases are unique to women: oral contraceptives, early menopause due to removal of the ovaries, and the hormonal changes of menopause. On

High blood pressure is one of the risk factors for coronary heart disease. About 27 percent of women have hypertension (high blood pressure) or are on anti-hypertensive drugs.

the positive side, a substantial amount of evidence suggests that postmenopausal women who take estrogen have lower risks for cardiovascular disease. The estrogen seems to raise levels of the "good" cholesterol.

Women face more danger than men from first heart attacks. The first one is fatal 39 percent of the time for women, compared with 31 percent for men. And studies suggest that women who have had heart attacks do less well with treatment, such as coronary bypass surgery. It appears, however, that the adverse effects in women may be due to their smaller body size rather than to biological differences between sexes.

Women make up about two-thirds of the population over 65, the age where cardiovascular diseases occur most frequently. That population will continue to grow. Unless ways are found to reduce the underlying atherosclerosis and prevent the adverse consequences, such as heart attack and stroke, these diseases will remain a major public health problem for women.

"We're trying to educate and encourage more people to do research on (cardiovascular diseases in) women," Eaker said. "It's still the No. 1 killer."■

Lengthwise section of a normal artery compared with a blocked one.

LUPUS

Thirty years ago lupus—an auto-immune disease found primarily in young women—was thought to be a rare, frequently fatal illness.

Subsequent research proved that lupus is far more common. The Lupus Foundation of America estimates that 500,000 Americans have the disease, about one out of every 300 women. However, scientists have also found that the disease is far less life-threatening than it was in 1955, when the first prognosis study of lupus was written. Then, only half of lupus victims lived more than four years. Today 95 percent survive that long, and 80 to 90 percent live 15 years or more.

"Today the outlook has improved greatly," said Lawrence E. Shulman, M.D., Ph.D., director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. "Many patients can look forward to living a full life span."

The disease is formally called systemic lupus erythematosus. It is a chronic malady characterized by unpredictable flare-ups of joint pain, fever, and rashes. Patients may have a butterfly-shaped rash spreading over the bridge of the nose onto the cheeks. Some say this characteristic rash resembles the bite of a wolf, hence the name "lupus," which is Latin for wolf.

In lupus patients, abnormalities of the immune system cause it to attack healthy tissue. "The person who has lupus," Shulman said, "is allergic to his own tissues." It can also affect the lung lining, kidneys, brain, lungs, and heart. It is not contagious.

Lupus is nine times more common in women than in men, appearing most frequently in women during late adolescence and the 20s. Researchers, therefore, have turned to female hormones as a possible cause of the disease. Experiments using inbred strains of mice with lupus showed that female hormones do accelerate the disease while male hormones retard it. Also, studies in humans have found abnormal production of female hormones in women and men with lupus. Although the advances in hormone research have been promising, Shulman thinks other feminine factors, not yet identified, may be involved in causing the disease.

Investigators have found that heredity contributes to the development of lupus but is by no means the entire cause. For example, studies of identical twins have found that one twin may have lupus while the other does not. This suggests lupus may be triggered by other factors, possibly environmental, that have not yet been discovered.

NIH scientists have been studying genetic, immunological, and hormonal factors that might contribute to the development of lupus. They have been involved with developing better treatments, including an intravenous "bolus" technique for giving powerful drugs, such as cyclophosphamide. One large dose, or bolus, of the drug has proven to be effective against lupus and spends less overall time in the body, thereby reducing the side effects of chronic drug toxicity.

Lupus patients sometimes have a characteristic butterfly-rash over the cheeks and the bridge of the nose.

Most patients since the 1950s have been treated with corticosteroids, such as prednisone, which have greatly reduced the death rate from lupus. In addition, better diagnostic tests have helped doctors find the disease at earlier, more treatable stages and give more precise drug doses with fewer side effects.

Lupus remains a challenge. Scientists are still looking for factors—which may be many—that cause the disease and are developing better drugs and treatments. Said Shulman, "We still have a way to go."

Nevertheless, the outlook for the thousands of women with lupus remains relatively bright. "With good treatment and good followup, with a good doctor and the help of family and friends," Shulman said, "a patient can lead a relatively full and comfortable life."■

Diseases of the Older Woman

Osteoporosis

Osteoporosis, a condition in which the bones become porous and thin due to reduced bone mass, can make people's bones break at the slightest mishap or fall.

It is a condition afflicting women more severely than men, exacting a high toll in personal suffering and economic loss.

On the national level, osteoporosis:

—affects 24 million Americans, the majority of them women.

—is responsible for 1.3 million fractures per year, usually of the spine, wrist, or hip.

—costs the United States 7 to 10 billion dollars per year.

On the personal level, osteoporosis is debilitating and may contribute to death. It is responsible for 200,000 hip fractures per year in the United States, 84 percent of them in persons over 65 and a majority of them in women. White women are especially susceptible, and 15 percent will fracture a hip sometime in their life. Of these:

—20 percent will die within a year of injury.

—20 percent will still be institutionalized a year later.

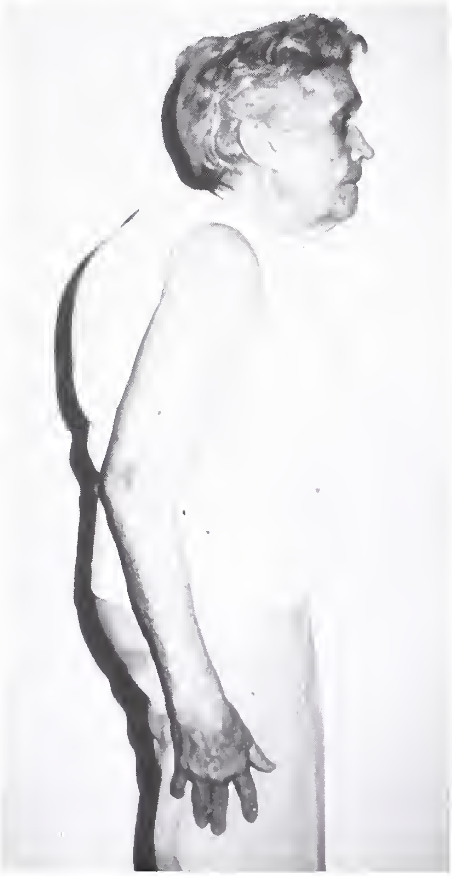
—30 percent will have reduced mobility, depending on aids such as a cane or walker.

Women also have a 15 percent chance of getting a wrist fracture and a 40 percent chance of having a compression fracture of the spine. Spinal fractures can result in intermittent pain and dowager's hump, a hunchback condition characteristic of older women suffering osteoporosis of the spine. Other fractures limit activity and increase chances of institutionalization.

"Osteoporosis is one of the major health problems in women," said Stephen Gordon, Ph.D., director of the Musculoskeletal Diseases Program at the National Institute of Arthritis and Musculoskeletal and Skin Diseases. "From the fact that women are living longer, it appears that osteoporosis is going to become more of a national problem."

Osteoporosis usually becomes evident after menopause, but scientists cannot yet predict with certainty which women will develop it. They do know it is more common in women with certain risk factors: early menopause, especially through surgery to remove both ovaries; being Caucasian; chronically low calcium intake; lack of exercise; being underweight; and possibly a family history of osteoporosis, cigarette smoking, and alcohol abuse. On the other hand, weight-bearing exercise and estrogen supplementation after menopause will help protect against the condition.

Osteoporosis is probably caused by several factors. Reduced levels of the female hormone estrogen with the onset of menopause certainly influences the course of the disease. Estrogen replacement therapy taken up to 10 years after menopause "pretty much flat out reduces the loss of bone," Gordon said. Estrogen is the only proven means of stopping bone loss, but it increases the risk of endometrial cancer, abnormal bleeding, or other complications. Estrogen is recommended for women at high risk for osteoporosis but low risk for estrogen side effects and who are willing to undergo periodic checkups. The National Center for Nursing Research is funding a study to find ways of helping women weigh the risks of estrogen treatment and make an informed decision.



Osteoporosis can sometimes result in the presence of a "dowager's hump", which is the result of collapse of the spinal vertebrae.

Calcium deficiency also contributes to osteoporosis. The mineral's role in bone development is being studied by scientists who have found that high calcium intake during the growth spurt of adolescence may produce increased bone mass that protects against fractures in later life. Persons should take adequate amounts of calcium throughout life, but especially during youth. When they are old, their bodies will be less able to absorb it. NIH experts recommend 1,000 mg of calcium per day for young women, 1,500 mg per day for women after menopause, and 1,000 mg per day for women taking estrogen.

Calcitonin, a synthetic form of the hormone produced by the thyroid gland, can reduce bone loss in some people and is considered safe. It was approved by the Food and Drug Administration in 1984. But for the present, its high cost, the fact that it must be injected and the uncertainty of long-term benefits have limited its use.

Studies supported by the National Institute on Aging (NIA) and others suggest that vigorous physical exercise, such as rowing, bicycling, and weightlifting, may increase bone strength in postmenopausal women. Furthermore, it is clear that inactivity leads to bone loss. Scientists believe that activity involving the muscles working against gravity, such as walking or jogging, may help reduce bone loss.

Sodium fluoride, taken in conjunction with calcium, is one of the few substances shown to increase bone formation. For that reason, it may help people already suffering from osteoporosis. But the high dose levels required can produce worrisome side effects, such as stomach pain and nausea, and the treatment is still experimental. Researchers supported by the NIAMS are now investigating—in a large clinical trial—fluoride's effectiveness in preventing fractures and the potential risks involved in its use.

The problem of osteoporosis is aggravated by falls. Researchers, therefore, have investigated certain conditions—such as reduced hearing, leg strength, mobility, mental status, distance vision, and back flexibility—that contribute to falls. They have found that the likelihood of falling rose with the number of disabilities and that almost all recurrent fallers had poor distance vision, poor back flexibility, and decreased strength in the lower extremities. Scientists hope that potential fallers can be identified by simple balance and movement tests and routine data from medical examinations. They might then be helped before they fall and suffer a serious, debilitating fracture.

NIA also suggests that people minimize the risk of fractures by minimizing hazards in the home. They can avoid slippery floors and loose throw rugs, remove objects that might cause a fall, provide adequate lighting, add handles or nonslip bottoms to bathtubs, and install railings on stairways inside and outside the home. They can also avoid actions, such as lifting while bending forward or lifting heavy objects, that stress the bones unduly.

With the number of older people rising in the future, osteoporosis will certainly become more prevalent among women in the United States. Moreover, these women will have already passed through adolescence, where they often consumed more soft drinks and less milk products. Fortunately, exercise has been more popular among this group than in previous generations. And there is hope that exercise plus advanced treatments involving estrogen, calcium and other promising factors will reduce the impact of osteoporosis on older generations of American women. ■

Incontinence

Incontinence—the distressing, accidental loss of urine or feces—can affect anyone, male or female, from infants to young adults to older people. By many, it is considered a natural consequence of aging, an irreversible loss of dignity especially common in older women.

This condition, however, is not a natural part of growing old. It can, in many cases, be prevented, controlled, or handled with little or no loss of dignity.

"The majority of older people don't become incontinent, and it shouldn't be considered inevitable," said Evan Hadley, M.D. chief of the Geriatrics Branch at the National Institute on Aging (NIA). And of those who do suffer incontinence, he added, the percentage that can be treated "is pretty high."

More than 30 percent of American women over 60 have some trouble with incontinence, from a few drops to a significant loss of urine. Fear of having an accident in public keeps many of them from going out, contributing greatly to their isolation and loneliness. In nursing homes, incontinence afflicts about 45 percent of residents and adds an estimated $1 billion a year to the cost of nursing care.

Incontinence is a symptom of something gone wrong elsewhere in the body. In many women, it is a structural problem, such as an abnormally positioned bladder, that can be cured surgically. Some patients can be helped by prosthetic devices that aid or replace muscles controlling urine flow. In other patients, incontinence may be responsive to drugs.

Incontinence can occur at any age. Research aims at helping older women avoid accidents by teaching behavioral techniques.

In women of all ages, physical exertion or sneezing or coughing may cause loss of urine known as stress incontinence. Pelvic floor exercises, or Kegel exercises, can alleviate this problem in younger and older women. These exercises, which involve strengthening muscles around the vagina, usually produce results in 6 to 12 weeks.

In older women, urge incontinence becomes more common. The woman has a strong urge to urinate but is unable to hold it long enough to reach a toilet.

Incontinence is often related to loss of mobility—for example, a women with normal bladder control is physically unable to get to a toilet. Other times it is caused by dementia, the loss of mental alertness that would otherwise forestall an accident.

In the past, treatment focused on managing the condition rather than controlling it, much as one manages an infant's involuntary urination with diapers instead of controlling it with toilet training. In fact, a large industry has developed producing materials and garments to keep incontinent elderly people dry and free from skin irritation and bedsores.

Today's research aims at helping older women—or the people who care for them—control incontinence to avoid accidents, and scientists are investigating a number of promising behavioral techniques:

—Bladder training teaches people to void at predetermined times to reduce the likelihood of an accident. The method aims at gradually increasing intervals between voiding to correct the habit of voiding too frequently, improve voluntary control, and increase bladder capacity.

—Biofeedback has been successful in treating stress and urge urinary incontinence and fecal incontinence. Patients strengthen and train muscles that control incontinence, using a biofeedback device to report how well those muscle are responding. For example, the technique was used in an NIA treatment program that helped outpatients improve incontinence control, on average, by more than 75 percent. Researchers have proposed a similar program for institutionalized elderly people who are incontinent.

—Prompted voiding uses positive reinforcement to achieve better bladder control. The method offers some hope of helping incontinent patients with severe dementia or mobility problems.

The NIA and the National Center for Nursing Research are funding several studies on dealing with the treatment of incontinence through biofeedback, bladder training, exercise, and knowing about individual voiding patterns. NIA's Laboratory of Behavioral Sciences at the Gerontology Research Center in Baltimore has produced a videotape to help teach nurses and other health care providers how to train patients to use incontinence-control skills at home. Research is also continuing on improved drug and surgical treatments for incontinence.

There are women whose incontinence can only be handled with traditional management techniques, such as using porous, absorbent bedpads to keep skin and bed clothes dry. But the number of these cases will diminish as better control techniques are developed.

In general, however, there remains the problem of putting research discoveries into everyday use, Hadley said. Many health-care professionals have not been trained to use more recent advances when dealing with incontinence. "There's a big gap between what we know about incontinence and the average state of practice across the U.S.," he said. Many patients are not getting treatment or are being poorly treated." ■

Alzheimer's Disease

Mrs. H. chats pleasantly and coherently about the weather, the clothes you are wearing and a recent car trip she took—but she can't tell you who you are or where she is.

She speaks lovingly of her husband—but she doesn't remember that he died seven years ago.

She was born in 1915 and is 73 years old this year, 1988—but she tells you she was born in 1902, is 90 years old and that this is 1954.

Mrs. H. is one of some 2.5 million Americans—the majority of them women—who suffer from Alzheimer's disease, the most relentless and devastating of old-age dementias. Three years ago she began to forget things, but friends ignored her problems, wrote them off as minor upsets or simply called them "just old age." Gradually her memory became worse—particularly about recent events—and her problems more difficult to explain. She became irritable, confused, easily distracted and began to show poor judgment. Eventually Mrs. H. will be totally unable to care for herself. And, because she is widowed and her only child lives 1,000 miles away, she is likely to spend her last days in a nursing home.

Alzheimer's disease is no longer regarded a natural consequence of aging, as it was thought only a decade ago. But it does affect a substantial number of older women.

"Alzheimer's disease increases in prevalence with age, and since women tend to live longer than men, you tend to have a large population of women with the disease," said Andrew Monjan, Ph.D., acting associate director of the Neuroscience and Neuropsychology of Aging Program at the National Institute on Aging (NIA). "The problem is getting worse because the U.S. older population is growing."

More than half the people throughout history who ever survived to age 65 are alive today, and as many as 10 percent have Alzheimer's disease. The majority of the victims are over 80, an age where women outnumber men nearly two to one. The direct and indirect costs of the disease add up to nearly $90 billion a year.

Women bear additional burdens caused by Alzheimer's disease. Since they are usually the primary caretakers of the family sick, women take on the extra work of looking after spouses, parents, and siblings who suffer this disabling disorder. And, because they live longer than men, women often outlive husbands who might care for them should they get the disease.

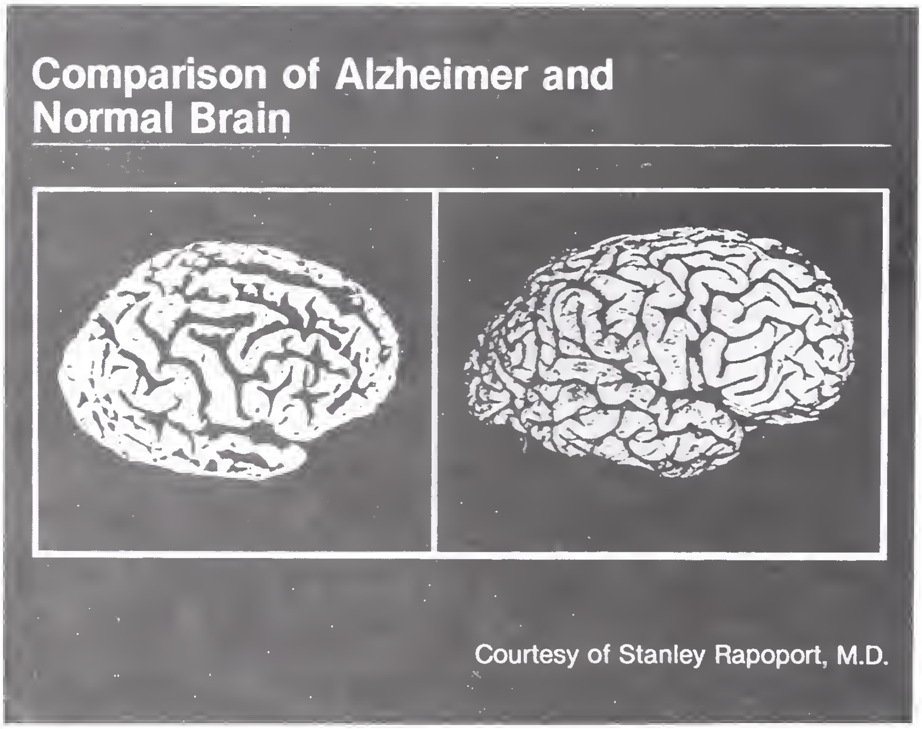
Twenty years ago, Alzheimer's was considered a rare disease, but today scientists know it is quite common. Only in the past 10 years has much research been focused on the disease, and many questions remain. Scientists are not sure whether the prevalence of the disease is increasing or whether the rate is stable and physicians are simply getting better at early diagnosis. They do not know whether particular groups of people get it more frequently than others. And they do not know its cause.

The disease was first described in 1906 at a German medical meeting, where Alois Alzheimer recounted the history of a 51-year-old patient. The woman's problem began with memory loss and disorientation, became complicated by depression and hallucinations, and ended with severe dementia and death. An autopsy revealed that her brain had severely shrunk and its cortex, or outer layer, was marked by a clumping and distortion of nerve-cell fibers. These tangles are a hallmark of Alzheimer's disease.

Today more than 80 years after Alzheimer's discovery, an autopsy is still the only definite way to diagnose the disease. But that should change. NIA-supported scientists have discovered in the brains of more than two dozen Alzheimer's victims an abnormal protein, called A–68, that could be the key to a diagnostic test. The largest concentrations of A–68 were found in the cortex as well as in the hippocampus deeper in the brain. Both areas are vital to memory and other mental functions that are severely damaged by Alzheimer's disease. The scientists later found A–68 in the cerebrospinal fluid of eight out of nine patients presumed to have Alzheimer's disease, but not in the fluid of 12 healthy people. If this work is corroborated—and a simple, practical test developed—doctors may soon be able to check for Alzheimer's disease in living patients by testing their spinal fluid for A–68.

Finding the cause of Alzheimer's disease is proving difficult, Monjan said. "It may turn out that Alzheimer's disease, like cancer, is not a uniform disease," Dr. Monjan said. "It may have different causes, such as genetics, the environment, or both."

Researchers suspect that heredity plays a role when the disease afflicts people under 60 and progresses quickly. They also think that environmental factors, such as toxins or infection, may be influential when Alzheimer's strikes people over 65 and develops more slowly. But some cases may occur when an inherited "predisposition" for the disease is activated by something from the environment.



Comparison of Alzheimer and Normal Brain

Courtesy of Stanley Rapoport, M.D.

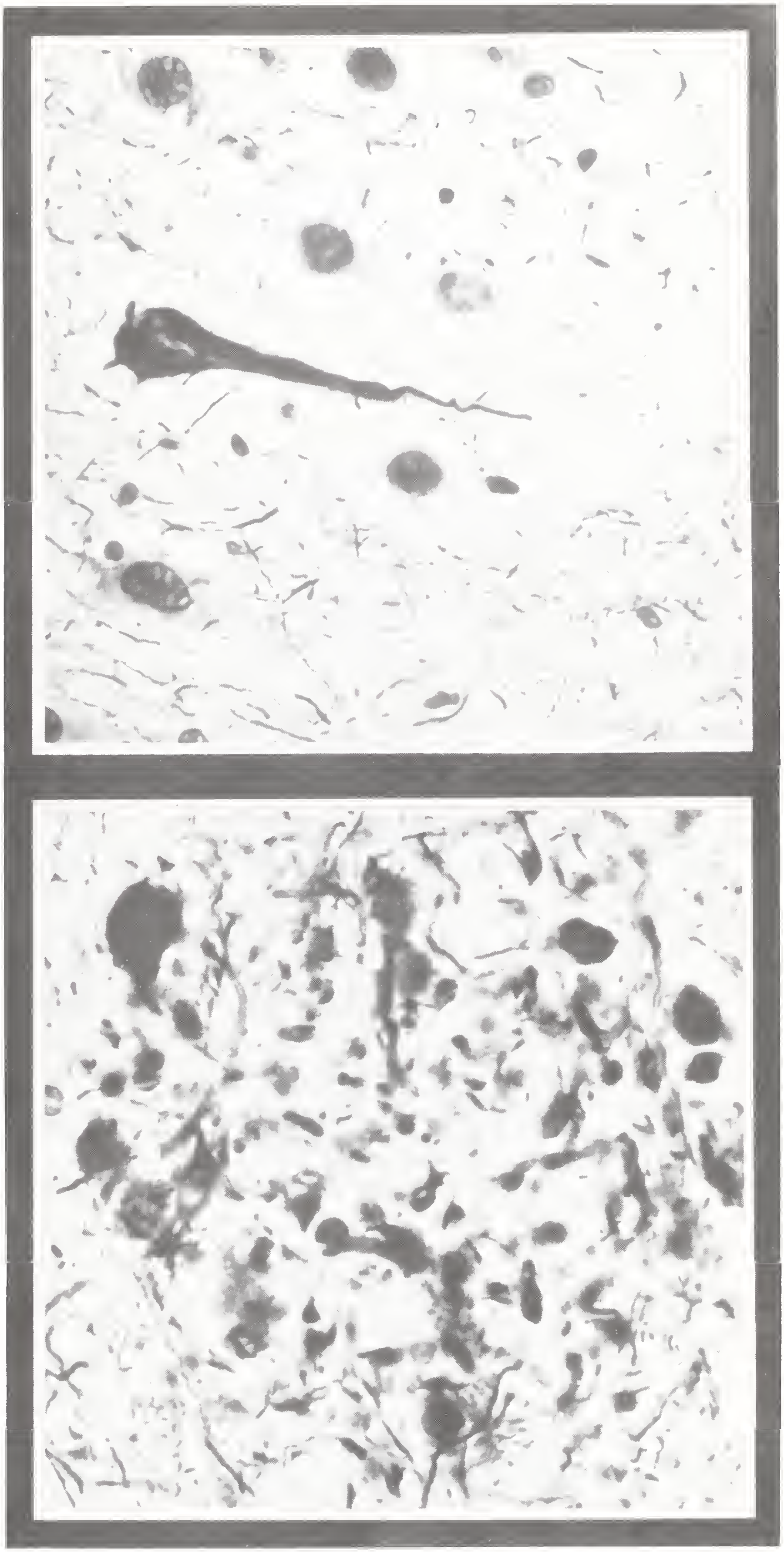
An atrophied brain (left) of an individual who has died from Alzheimer's disease compared with the brain of a healthy individual.

Preliminary research looking for a genetic basis for Alzheimer's disease had proposed a link to Down syndrome. The presence of a protein seen in healthy people, but found in abnormal amounts of starchlike amyloid fibers, is peculiar to patients with either disorder. Scientists from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) working with French researchers found that the gene that makes the amyloid protein seemed to occur three times, instead of the normal two, in the same critical area of chromosome 21 in both Alzheimer's and Down's patients. Recently, Massachusetts scientists were unable to duplicate this work. Questions remain about the presence of amyloid in the brains of Alzheimer's patients and whether it plays an important role in the development of the disease.

An important strategy for treating Alzheimer's disease is evolving from new knowledge about chemical functions in the brain. As early as 1976, NIH scientists established that Alzheimer's is marked by a serious defect in acetylcholine, one of the chemicals that brain cells use in communicating with each other. Since then, scientists have used drugs, such as physostigmine, to manipulate brain chemicals in hopes of restoring the devastating memory loss associated with Alzheimer's disease. Preliminary tests—conducted by the NIA and others—of a potentially promising drug, called THA or tetrahydroaminoacridine, revealed that THA may have unpleasant and potentially harmful side effects. Investigators are carefully monitoring patients to determine the safety of the drug.

Since the late 1970s, when large-scale research began, scientists have learned much about the molecular genetics of Alzheimer's disease. Today they are refining diagnostic procedures and testing treatments. Can a cure be far in the future?

"I would rather be upbeat on the question," Monjan said. "Maybe not a cure, but certainly a better treatment. ■



(right)

The Alzheimer brain is marked by two distinctive changes: neurofibrillary tangles (top) and neuritic plaques (bottom). Neurofilaments in the cell bind together into neurofibrillary tangles. These changes can be linked to cell death. Nerve cell endings degenerate leaving "senile" plaques in the brain and blood vessels. A key element of these plaques is amyloid, a protein that accumulates in excessive amounts in the Alzheimer brain.

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Special Issue: Toward a Better Tomorrow

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from NIH

October/November 1989

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Results from NIA-supported studies now allow us to identify older individuals at risk of falling and to define situations where falls might be prevented. See pg. **4**

Cover and inside illustrations by Margaret Georgiann, MAPB, NIH

About the issue:
Toward a Better Tomorrow

Aging is often thought of as an island unto itself. It's as if one day you awaken to find you are suddenly old. In fact, this is the greatest myth regarding age. Aging is part of a continuum, a gradual process, which includes all stages of the life cycle.

How one ages depends upon several factors. First, most scientists believe that genetics play a role. Second, environmental assaults, such as unclean air, may have an influence over how we age. Admittedly most people have little control over these two factors. The third aspect, lifestyle, plays an important role throughout life, and plays a particularly important role in the later years. It is here that an individual can take some measure of control over her/his destiny.

A high priority at the National Institute on Aging is to identify those lifestyle factors that influence the quality of late-adult life. Ultimately we hope to convince people of the importance of adopting healthier lifestyles to enable them to remain active and independent throughout their days.

The articles in this issue of *News and Features* were included specifically because they provide information to improve the quality of future years. Through education and awareness we can all strive toward a better tomorrow.

T Franklin Williams

T. Franklin Williams, M.D.
Director, National Institute on Aging

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As they grow older, many people are affected by a reduction in the senses of taste and smell. NIA researchers have developed some ways of managing the so-called "chemosensory" disorders. See pg. **6**

The Fallacies of Food Fads for Older People

Barbara Katzman, Public Affairs Specialist, NIA and Dr. Ann Sorenson, Health Scientist Administrator, NIA

Mrs. A suffers from osteoarthritis. She has tried myriad drugs to lessen the debilitating effects of the disease. Some worked marginally well, others were ineffective, and still others made her feel ill. One day she sees a testimonial on television promoting alfalfa tablets to reduce pain caused by arthritis. Mrs. A eagerly purchases the remedy.

Mr. B is 80 years old. Each winter for the past five he has endured a bout of pneumonia. He knows that this is a potentially life-threatening illness and therefore tries all the new cures advertised in the tabloids found at the supermarket checkout. He estimates that he is spending 10 percent of his Social Security check to find a cure.

Aging is a mysterious, sometimes fearful, phenomenon to many people. Some do indeed experience illness, loss of independence, or a forced change of lifestyle. The pain and despair associated with disability drive many people to seek untested "cures" from unorthodox sources. Patients may perceive their doctors as callous or modern medicine as too complex and expensive. For these and other reasons, older people are special targets for health fraud and faddism. In fact, an estimated 60 percent of health fraud in this country aims at the elderly population.

Definitions from the Surgeon General's Report

In a 1988 report (The Surgeon General's Report on Nutrition and Health), Surgeon General C. Everett Koop defined dietary fads and fraud as any "abuse that occurs as the result of the misleading claims for traditional foods, dietary supplements, and dietary products and of the deceptive promotion of other food substances, processes, and devices."

Food faddism was defined as a dietary practice based upon an exaggerated belief in the effects of food or nutrition on health and disease.

Food quackery is the promotion for profit of special foods, products, processes or appliances with false or misleading health or therapeutic claims.

There are many different types of health faddism directed at older people. Fad diets and vitamin supplements are among the most common.

There are many potential dangers associated with choosing treatment that lacks a sound scientific basis or for which the science is inappropriately interpreted. Perhaps most obvious, a person who embarks on a course of self treatment of dubious benefit may no longer be receiving reliable health care. The new method of treatment also may be useless and/or, ultimately, harmful. "Special" preparations also can be expensive, an important consideration for people on fixed incomes.

Vitamin Supplementation

There are many different types of health faddism being directed to and adopted by older people. Perhaps the most profitable from a marketing standpoint is vitamin supplementation. Thirty seven percent of American adults consume a daily multivitamin, fueling a more than $2 billion industry. Generally, these supplements are unnecessary for people of any age.

Dr. Koop advises that, because the Recommended Dietary Allowances (RDAs) were developed for young, healthy adults, we do not know if or how this standard might differ for the heterogeneous older population. In most cases, a well-balanced diet should supply all that is necessary to meet nutritional needs. However, some older people cannot, or will not, consume a diet that provides an adequate supply of essential nutrients. Others may have a condition or disease that is known to cause an alteration in nutrient requirements. In these cases, vitamin supplements should be prescribed by a health care professional. It should be noted that megadoses of some vitamins ("megadose" is defined as 10 times the RDA) can be toxic and cause severe health problems. For example, the RDA for vitamin D is 400 I.U. (international units). At 2,000 I.U., well below the megadose range, some people experience adverse reactions including nausea and irritability. In severe cases, vitamin D poisoning may cause mental retardation and kidney damage. Toxic levels of vitamin A may cause loss of hair and rheumatic pain.

Most nutrition experts agree that random use of vitamin supplements should be discouraged for the general population. Unfortunately, it is often the person who would benefit most from a supplement who neglects to seek medical attention because of financial considerations or medical fears. Indeed, the National Health and Nutrition Examination Survey II (NHANES II), supported by the National Institute on Aging (NIA), found that those in need of vitamin supplements are the least likely group to receive them.

Food Fads

Since many doctors are now advising people of all ages to control weight in order to decrease the risks and complications of such chronic disorders as heart disease, fad diets are as popular as ever. The grapefruit diet, in which grapefruit is purported to burn off fat, has no basis in scientific fact. Some food fads are particularly dangerous, or even lethal. For example, the highest level of the Zen macrobiotic diet, which recommends that a person eat only whole grains and limit water to 1/2 pint per day, can cause nutritional deficiencies, dehydration, starvation, and death. Money spent on food fads would be better spent on competent and reliable health care.

Dr. T. Franklin Williams, director of the NIA, believes that health fraud is a very serious problem for many older people. "Many substances or theories, often the object of legitimate scientific studies, are misused by faddists or charlatans to add a scientific gloss to an otherwise dubious commercial project. . . . The evidence that any of these is beneficial as claimed is slim and often based upon erroneous interpretation of scientific information."

The promotion of superoxide dismutase (SOD) as an anti-aging remedy is a perfect example. SOD is a naturally occurring enzyme found in all organisms which use oxygen to obtain energy from food. NIA animal studies show that longer-lived species naturally possess more SOD than do animals of shorter lifespans. Contrary to claims by faddists, however, this does not imply that taking SOD orally is advantageous. In fact, oral supplements of SOD are of no use since they are digested before body cells can use them. Other examples of faulty health claims abound: bee pollen as a source of sexual energy, lecithin to self-treat memory loss, gerovital-H3 to treat everything from self-diagnosed depression and hearing loss to general aging, and alfalfa tablets for the treatment of arthritis.

If It Sounds Too Good To Be True It Probably Is

It is important to be wary of absurd claims, outrageous treatments and miracle cures and to seek assistance from reputable sources. Most health care professionals are trained to offer sensible advice regarding nutritional problems. Up-to-date government documents, which report the best data available, also are reliable sources. An informed public is the best guarantee that unethical practices and false advertisements are unsuccessful.

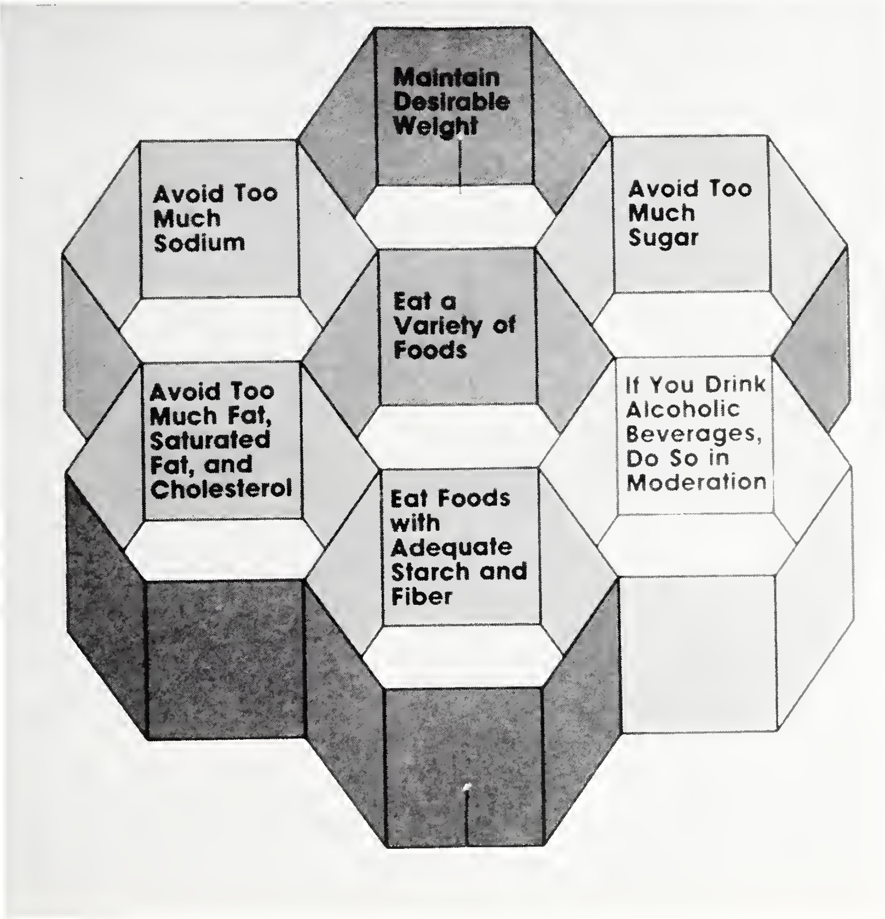
The Federal government plays an active regulatory role in protecting the public from false health claims: the Food and Drug Administration, the U.S. Postal Service, and the Federal Trade Commission are involved with identifying and prosecuting health fraud. There also are ways individuals can protect themselves against false health promotion and disease prevention claims.

Suspect a fraud when:

- Common foods are given healing powers. Examples include peaches with special intestinal cleansing properties and garlic pills which purportedly cure a host of illnesses.
- Claims are made that certain foods cause adverse effects on health and therefore should be completely avoided. Examples include chocolate, viewed as an unhealthy stimulant and mustard, a powerful irritant. A variation of this is the claim that eating raw fruit and vegetables at the same meal should be avoided because it "confuses" the enzyme producing glands in the body.
- Claims for remarkable cures associated with bizarre diets or food combinations. Often these diets reappear years later with different promises. A vinegar and honey brew was touted as a cure for heart disease and later recycled as an anti-aging compound that would also reduce wrinkles.
- Statements claim a product is "natural" or "organic" and therefore of superior quality. Natural foods react no differently in the body than "regular" foods but may cost a lot more.

If the goal of an individual is to live a longer, healthier life, there are scientifically proven ways to assist in this effort. These include eating a well-balanced diet (as recommended in the Dietary Guidelines published by United States Department of Agriculture and the Department of Health and Human Services), embarking on an exercise regimen approved by a health care professional, quitting smoking and limiting alcohol intake, if any. Receiving regular medical checkups, wearing seat belts, and staying socially active also contribute to a longer, healthier life.

No doubt, special health problems may necessitate specific dietary requirements and major alterations in lifestyle. Ideally, these changes should be prescribed by a team of health professionals including a physician and a registered dietitian. While it is true that there are still many unknowns in the area of nutrition for older people, and that more research is necessary to close these gaps, the importance of making informed decisions about nutrition, based on an understanding of one's own needs, cannot be overstated. ■


Maintain Desirable Weight
Avoid Too Much Sodium
Avoid Too Much Sugar
Eat a Variety of Foods
Avoid Too Much Fat, Saturated Fat, and Cholesterol
If You Drink Alcoholic Beverages, Do So in Moderation
Eat Foods with Adequate Starch and Fiber

Good nutrition is a balancing act. The seven Dietary Guidelines, used together, can be helpful in selecting a healthful diet.

A Delicate Balance: Promoting Independence and Preventing Falls in Older Adults

Karen McCrory Pocinki

The call came in the middle of the night. "Your grandmother is in the emergency room. She fell and broke her hip." This was not my grandmother's first fall, but it turned out to have the most serious consequences. At first, she tripped over the throw rugs in the living room. Sometimes, her unsteady gait caused her to "pitch backward," as she called it, and lose her balance. Negotiating stairs unassisted became a problem.

The first few falls produced bruised arms and legs, a twisted ankle, and muscle aches and pains—nothing serious. Then, she stumbled on the stairs and cut her shin, which required 26 stitches. And finally, in the middle of the night on the way to the bathroom, she fell and broke her hip.

My grandmother is not alone. Each year, approximately one-third of all persons 65 years of age and older who live at home fall. A very common type of accident in older Americans, falls cause more than 200,000 hip fractures annually. Falls contribute to 40 percent of nursing home admissions, and they are the leading cause of accidental death in men and women over age 85.

Although some falls have a single, obvious cause, researchers believe that most falls are due to a combination of several risk factors, including the use of sedatives; changes in mental status, vision, hearing, muscle strength, reflexes, and coordination; and environmental hazards. In addition, studies suggest that balance and gait disorders are associated with an increased risk of falling.

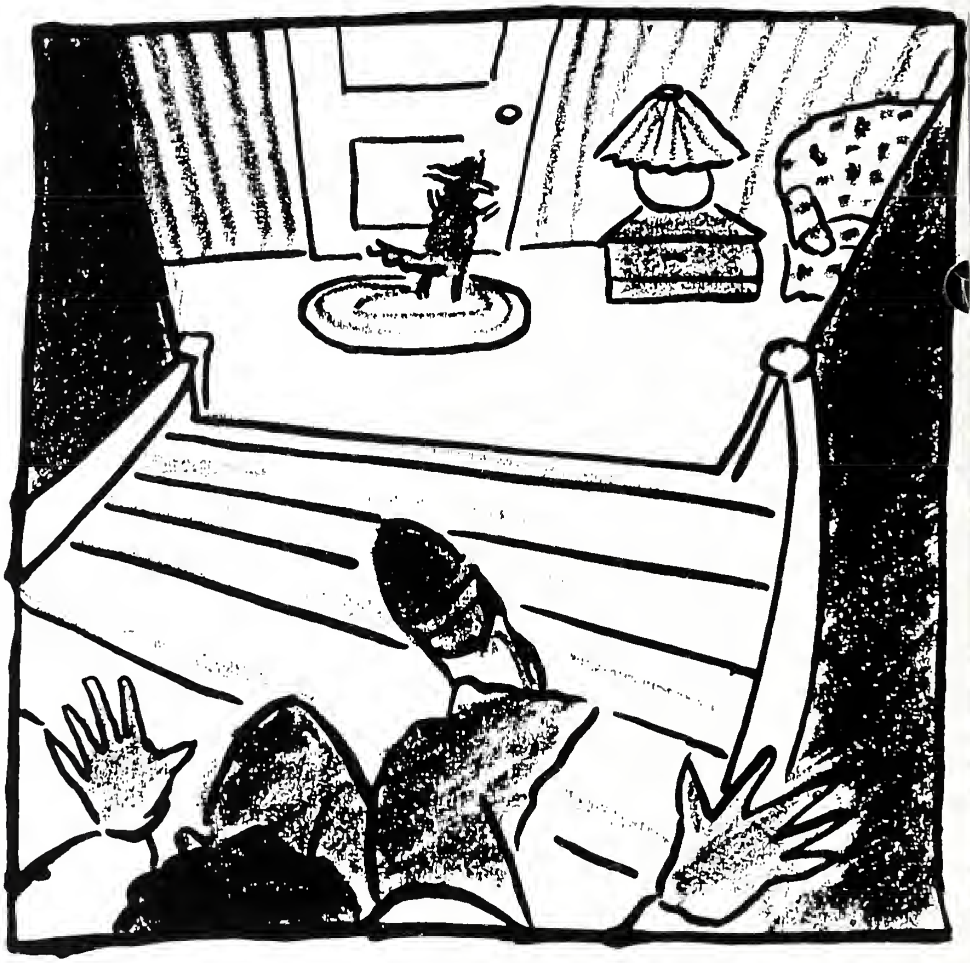
Research supported by the NIA focuses on determining the extent to which physical frailty and risk of injury may be reduced in older people. To learn which older individuals are at greatest risk of falling, Dr. Mary Tinetti of the Yale University School of Medicine studied more than 300 people 75 years of age and older who were living in the community. At the beginning of the study, the participants underwent a thorough evaluation, including standardized measures of their physical and mental health, strength, reflexes, balance, and gait. Participants recorded their falls in a diary and were called every other month to discuss the number of falls and the circumstances surrounding their occurrence.

During the year the study was conducted, 32 percent of the participants fell at least once. Of those who fell, 24 percent were seriously injured, including 6 percent who suffered fractures. Twenty-six percent of those who fell reported that they had curtailed activities such as shopping or housecleaning because of their fear of falling.

Dr. Tinetti found that significant risk factors for falling included sedative use, cognitive impairment, lower extremity disability, foot problems, and balance and gait abnormalities. She also discovered that the tendency to fall increased with the number of risk factors present, from 8 percent for individuals with no risks to 78 percent for those with 4 or more risk factors. Her research suggests that it may be possible to prevent falls by modifying even a few of these risk factors.

In a related study, Dr. Marjorie Woollacott of the University of Oregon examined postural control in older people. Postural instability—also called excessive sway—is a movement abnormality commonly seen in older persons.

To maintain balance, an individual makes certain postural adjustments before moving. These adjustments compensate in advance for changes in balance. In her study of the influences of aging on postural responses, Dr. Woollacott found that older people take longer to make postural



Each year, approximately one-third of all persons 65 years of age and older who live at home fall. Falls cause hip fractures, contribute to nursing home admissions and are the leading cause of accidental death in men and women over age 85.

adjustments before they initiate voluntary movement.

Two groups of subjects (15 young adults with an average age of 26 years and 15 older individuals with an average age of 71 years) were asked to push or pull on a handle placed in front of them at chest height while they stood on a platform. Individuals with any history of neurological impairment were excluded from testing. Dr. Woollacott measured muscle responses in the subjects' arms and legs. Previous studies indicated that young adults use certain leg muscles to maintain their balance when pushing or pulling on a handle while standing. The contraction of the leg muscles prevents falling by compensating in advance for changes in the center of gravity caused by pushing or pulling on the handle.

Dr. Woollacott found that postural muscle response (leg muscle contraction) was significantly slower in the older group. In addition, upper arm muscle response (reaction time) was slower in the older adults. Dr. Woollacott's research points to changes in older adults that might make them unsteady on their feet when reaching for or lifting objects and thus at greater risk of falling.

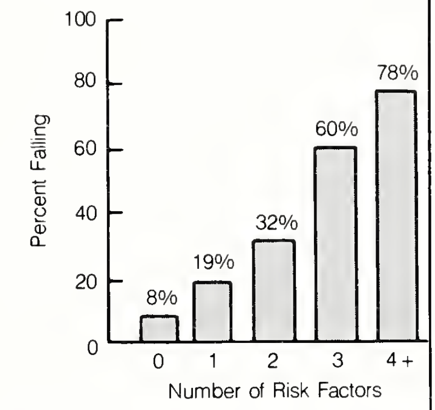
To learn more about lower extremity disability and falling, Dr. Leslie Wolfson of the Albert Einstein College of Medicine studied knee and ankle strength in a group of nursing home residents with a history of falling. In this NIA-funded study, Dr. Wolfson observed that muscles were significantly weaker in those who fell, with the greatest deficits found in the ankles.

Ankle weakness appears to be an especially important factor underlying poor balance. Poor function of ankle muscles makes it difficult to adjust the center of gravity rapidly enough to prevent falling. Although deterioration of lower extremity strength and gait is seen in healthy older people, gait is particularly compromised in those who are ill or homebound. In those confined at home, researchers have seen an association between tripping and a decline in gait speed and a decrease in step size, both of which may be related to lower extremity weakness.

Dr. Wolfson measured knee and ankle strength in one group of older individuals (average age 82 years) who had one or more unexplained falls during the previous year and in a second group of older people (average age 84 years) who had not fallen. The older individuals who fell had severe impairments in their overall ankle strength. Dr. Wolfson also noted a decrease in the speed of ankle motion, which has been related to the slower walking speed of individuals who fall.

The greater severity of injuries suffered by older people combined with longer recovery periods make falls a serious threat to the health and well-being of older individuals. In addition to physical injury, those who fall also experience psychological stress, including loss of self-esteem and self-confidence. Fear of falling leads to diminished activity and increased dependency, limiting the quality of an older person's life. Research findings now allow us to identify those older individuals at risk of falling and to define situations where interventions might prevent falls from occurring. ■

Occurrence of Falls According to the Number of Risk Factors.



	0	1	2	3	4+
No. Falling	4	20	30	35	18
No. Subjects	51	106	94	58	23

Tinetti ME, Speechley M, et al. Risk factors for falls among elderly persons living in the community. The New England Journal of Medicine 1988; 319:1701–1707.

Inglin B and Woollacott M. Age-related changes in anticipatory postural adjustments associated with arm movements. Journal of Gerontology: Medical Sciences 1988; 43:M105–113.

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On Balance: A Safer Way To Fall

Margo Warren

The fear of falling and suffering serious injuries such as hip fractures prevents many frail older people from doing the very thing that would help them most—undertaking exercise or rehabilitation programs. A new falls intervention device that reduces the force of falls by up to 98 percent promises to help restore an older person's confidence and physical strength.

A grantee of the National Institute on Aging (NIA), Dr. David P. Colvin, president of Triangle Research and Development Corporation in Research Triangle, N.C. has developed an innovative device called FALL-SAFE™, which offers people a way to fall safely. The system combines a ceiling-mounted trolley with a specially designed garment to cushion a frail, older person or a patient in physical rehabilitation from the potentially devastating consequences of a fall.

Dr. Colvin developed FALL-SAFE™ after more than 10 years of engineering development. Prototype systems are now being evaluated at the Hillhaven Convalescent Center in Chapel Hill and at the Rehabilitation Department at Duke University in Durham, both in North Carolina.

The fail-safe system responds immediately to a fall and applies a safe braking force to gently catch and lower the user to the floor. A special vest-like garment, UniSupport™, then provides a gentle, even-stress distribution to the torso. The system can be used by older people for safe walking exercise and by patients as they get in and out of wheelchairs. FALL-SAFE™ is designed for use primarily in nursing homes, hospitals and rehabilitation centers. After a thorough testing period in these facilities, the system may be extended to home use.

According to Dr. Colvin, FALL-SAFE™ will also increase an older person's sense of independence and confidence through improved mobility and exercise, which are keys to maintaining bone strength.

Dr. Colvin was inspired to design FALL-SAFE™ after his own experience caring for older parents. "If older people don't exercise, they can fall and break their bones," said Dr. Colvin. He said FALL-SAFE™ provides a way for patients to exercise, and to fall with a minimum chance for injury.

Taste and Smell Disorders: Nothing to Sneeze At

Margo Warren

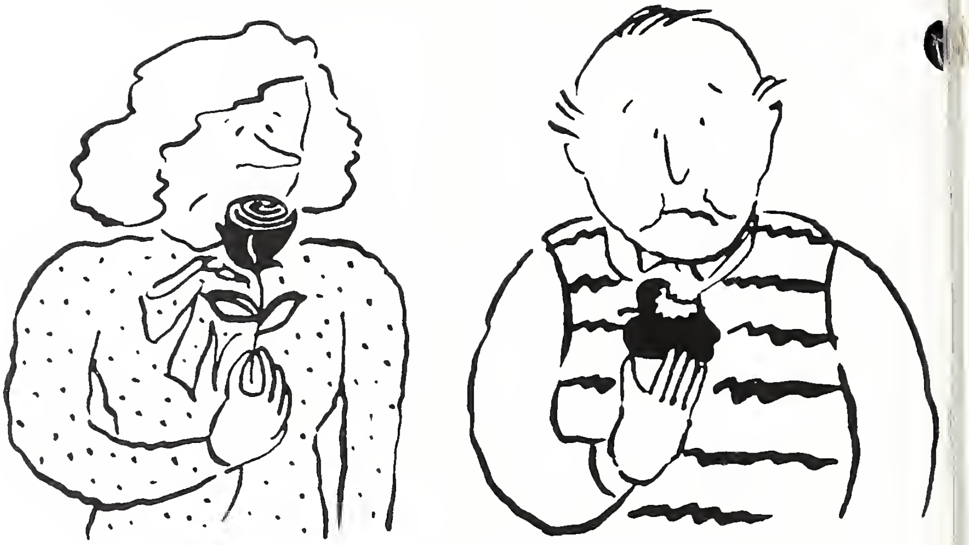
A pot of homemade spaghetti sauce is simmering on the stove. Lured into the kitchen by its aroma, you lift the lid off the pot and inhale the steam before you take a mouth-watering taste.

Many older people are deprived of this kind of simple pleasure. The aroma does not lure them into the kitchen, because they can't smell what's cooking. And once they sit down to eat, the food simply doesn't taste very good to them, certainly not as good as it tasted when they were younger.

Two million American adults, many of them over 65 years old, have taste and smell disorders. Their complaints are often treated as mere inconveniences. However the results have serious consequences:

- When the pleasure from eating disappears, there is a reduction in the overall quality of life, with an increase in depression and stress.
- Older people may become malnourished.
- In extreme cases, older people can become anorexic.
- The taste disorder can cause poor digestion by altering salivary flow and intestinal mobility.
- Lack of taste creates an inability to tell if food has gone bad, which can result in food poisoning.
- Losses in odor sensitivity can cause older people to overlook gas leaks or even the presence of smoke or fire in their homes.

Working with grant support from the NIA, Dr. Susan S. Schiffman of Duke University in Durham, North Carolina, has been studying the effects of diminished taste and smell in older people for almost 15 years, and has found a variety of causes: cancer and other diseases, drugs, radiation therapy, chemotherapy, head injuries and viral infections, as well as normal aging. The problem often goes away when a medical condition subsides or a treatment ends. But those disorders associated with the normal aging process are frequently there to stay. Taste and smell disorders are grouped under the heading of "chemosensory" which describes the ability to perceive chemical substances through the senses of smell and taste.



Many older people are affected by a reduction in the senses of taste and smell.

In her research, Dr. Schiffman documented that a common taste must be two and a half times stronger to register with a healthy older person than with a younger person. This taste "threshold," which becomes higher in older age (65 and older), refers to the concentration at which a taste becomes distinguishable from water. Cooked carrots, for example, would have to have more than twice as much salt in them for an older person to recognize a salty taste, as the same dish prepared for a younger person.

Problems begin when older people try to make up for diminished taste by adding excess sugar, artificial sweeteners or salt to their foods, which have been known to contribute to obesity, diabetes, bladder cancer, or hypertension.

Dr. Schiffman recently reported advances in treating the disorders and restoring enjoyment for food with simulated odor and flavor enhancers. She conducted a clinical trial using flavor enhancers to treat older anorexic patients in nursing homes and hospitals. She found that adding flavor enhancers successfully helped to counteract the chemosensory losses, to increase appetite, and to reverse the effects of anorexia.

Simulated carrot odor enhanced the appeal of carrots, and chicken aroma amplified the scent of plain chicken. Bacon flavoring spiced up the green beans, adding taste and odor but no fat or salt. According to Dr. Schiffman, the enhancers, mixtures of odorous molecules and flavor compounds, were effective in increasing appetites primarily because of the pleasure value they added to the food.

As part of the test, subjects 70–79 years old ate both plain and enhanced foods. Seventy-five percent of the 35 subjects preferred the food with the added flavor. Dr. Schiffman said the findings may help reduce malnutrition, which affects a significant number of older patients in hospitals, reducing their resistance to infection. Because flavors can be added to nutrient-dense foods, among others, older people may be more likely to choose a healthier diet with foods rich in protein, vitamins and minerals. For example, the addition of chicken flavor to chicken can help to reduce protein deficiencies.

The enhancers also allow a patient to eat a conventional meal rather than take special dietary supplements through expensive methods such as oral liquids, intravenous feeding, or nasogastric tubes. The pleasure provided by flavor and odor enhancers also helps to reduce depression, which can be a contributing factor to anorexia.

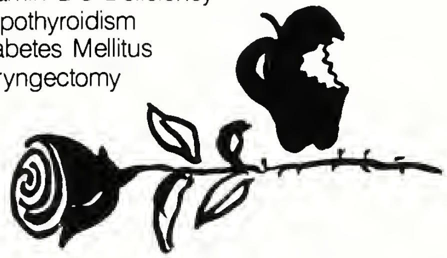
Dr. Schiffman cautions that more research is required before such enhancers will be available on the market shelves.

Losses in smell perception with age are even greater than those for taste. Anyone who has ever had a cold knows about the connection between the two senses: nothing tastes good when your nose is congested. In fact, an odor threshold can be as much as 12 times higher for an older person as a younger one. With aging also

Selected Disorders Affecting Taste and Smell

Taste and Smell:

Head Trauma
Multiple Sclerosis
Chronic Kidney Failure
Liver Disease (Including Cirrhosis)
Vitamin B-3 Deficiency
Hypothyroidism
Diabetes Mellitus
Laryngectomy



Taste:

Bell's Palsy
Cancer
Zinc Deficiency
Radiation Therapy
Hypertension
Influenza

Smell:

Parkinson's Disease
Tumors and Lesions
Sinusitis
Acute Viral Hepatitis
Laryngectomy

comes a problem in identifying odors. Several studies have shown a link between loss of sense of smell with Alzheimer's disease, which may be related to cell loss, amyloid plaques and neurofibrillary tangles found in the olfactory tract of these patients. The consequences of this reduced olfactory ability can be very serious.

NIA grantees Dr. Joseph C. Stevens, Dr. William S. Cain and colleagues at the John B. Pierce Foundation Laboratory in New Haven, Connecticut, conducted a study with the dramatic conclusion that many older persons are at high risk from household fires and explosions. The reason—they are unable to detect the odorant commonly added to propane gas by gas companies as a warning agent.

Because propane, as most gases, is odorless, an odorous substance called ethyl mercaptan is added to signal danger from potentially explosive gas leaks. In a study comparing 21 young people (18–25 years of age) and 21 older people (70–85 years of age), seven of the older people failed to detect the odorant at a concentration considered by fire department standards an "unacceptable" level of propane leakage. Three failed to detect the odor at a concentration so high that propane could explode.

In a second study, 50 of 110 people over 60 years of age failed to detect the odorant at a level considered adequate for safety. Six of 52 persons under 40 years of age also failed.

The investigators also ran tests for odor identification. Subjects were asked to sniff 10 common odors including rubbing alcohol, tea, and orange from unmarked containers. On the first round, subjects were asked to name each odor without prompts; on the second round, they could select the correct odor from a list of four alternatives. Without prompts, the younger group correctly identified an average of 5.62 odors out of the 10; the older group, 2.52 odors. When the odors were disclosed, the younger group identified 8.95 odors, and the older group 7.52 odors.

Drs. Stevens and Cain point out that the decreased ability to identify odors compounds the problem faced by older people when it comes to hazards in the home. "While it is one thing to detect a smell, it is another to identify it and act on it," the researchers say.

The study cited the perils associated with propane usage: 2,227 propane fires in 1984, reported by only one third of U.S. fire departments, resulting in 19 fatalities and 372 injuries. Many of the injured claimed to have smelled nothing before the explosion. It is not known how many of these fires involved people over the age of 65, or how many of them might have been prevented with proper diagnosis and treatment of a smell disorder.

While the report remarks that its results are "consonant with the finding of many investigators that aging often weakens the sense of smell," it adds that many older people fail to observe that the sense has weakened, and encourages more education on the topic.

Historically, the senses of taste and smell have taken a back seat to the more vital senses such as sight and hearing. But recent research sponsored by the NIA and elsewhere has pointed up the fact that these so-called "lesser" senses can cause an older person needless discomfort and poor health. Perhaps there will be increased recognition that taste and smell disorders are serious handicaps in their own right and indeed nothing to sneeze at. ■

Schiffman SS, Warwick ZS. Flavor enhancement of foods for the elderly can reverse anorexia. Neurobiology of Aging 1988; 9:24–26.

Stevens JC, Cain WS, et al. Aging impairs the ability to detect gas odor. Fire Technology 1987; 23:198–204.

Homeward Bound: Help for Older Stroke Survivors

Freddi Karp

When can I go home?

For an older person who has survived a stroke, this simple question can be the beginning of a complicated decision-making process for the patient, the family, and the health professional. NIA-grantees Drs. Gaylene Becker and Sharon Kaufman at the University of California, San Francisco have analyzed this decision-making process and developed a "road map" to help individuals consider all possible resources and roadblocks.

When a person has a stroke, the initial decisions are made under emergency conditions—there isn't much choice about how to proceed. Individuals are hospitalized and treatment begins immediately. However, once the individual has stabilized, a variety of choices face the patient and family. Should the patient go home, go to an intermediate care facility (e.g., a rehabilitation hospital), or to a skilled nursing facility? A comprehensive, high quality rehabilitation program can be critical to assuring the patient recovers as much function—both physical and cognitive—as possible. According to Drs. Becker and Kaufman, decisions about future care for stroke patients are influenced by such factors as the severity of the stroke, the financial resources of the family, the physical characteristics of the home, the willingness and ability of a family member to care for the patient, and the patient's rehabilitation potential.

Given that people almost always prefer to go home—even in the face of nearly insurmountable odds—it is of the utmost importance that family members consider their capabilities realistically. Drs. Becker and Kaufman suggest that this evaluation address four basic questions:

- What is the patient's recovery potential?
- What is the family's caregiving capacity?
- Will the patient be able to master the home environment?
- Would further rehabilitation in a hospital setting enhance the patient's functioning?

Responding to these questions requires the active and honest, participation of health professionals, the family, and the patient.

Going home

For an individual recovering from a stroke, going home can signal an important step toward a return to a normal lifestyle. For weeks (sometimes months) the patient has been actively engaged in his or her rehabilitation. S/he has worked with physical therapists to improve walking and gross motor skills, with occupational therapists to learn new self-care skills, and with social workers to plan for the social and economic consequences of the stroke. Now s/he is going home! The excitement attached to this accomplishment can frequently cloud the planning that must be done to assure that the return home will be successful for both the patient and the family caregiver.

Drs. Becker and Kaufman have developed a list of things to consider when planning for an older patient's return home:

1. Choose the day of discharge carefully. For example, if additional home services are necessary, select a weekday—preferably a Monday through Thursday.
2. If attendant care is needed, allow enough advance time to hire and train someone. This will assure that the attendant can start work on the day the patient returns home.
3. Make sure that all home modifications are completed and all new equipment is in place prior to the patient's arrival.
4. Arrange for extra help to make sure that the trip home goes smoothly.
5. Plan a quiet first day—visitors should be discouraged.
6. Establish a daily rhythm that approaches the patient's former rising, eating, and sleeping patterns.

Once at home, an older person recovering from a stroke may be faced with another crisis. The full impact of his or her disability may not have been appreciated until seen in the context of the home. Suddenly actions and behaviors previously taken for granted are difficult, if not impossible. At this point two things may occur—first, the process of grieving for what has been lost begins in earnest; second, the individual begins adapting to an altered life.

During this process, if the patient becomes depressed, inertia is the common response. Sometimes the patient will even stop performing those tasks that s/he is capable of carrying out. These dynamics affect the family caregiver as well, sometimes causing a breakdown in his or her ability to provide quality care. Therefore, it is crucial that much advance thought be given to the return home in order to avoid the possibility of failure.

According to Drs. Becker and Kaufman, patients with residual loss generally move through three basic stages:

1. Dealing with disability: Grieving for the loss of one's former self is an important part of any recovery. However, it may not be until the patient returns home that his or her loss becomes unexpectedly, and painfully, obvious.
2. Re-grouping: Individuals begin to redefine their possibilities and see how a new routine can replace an old one. The act of getting dressed independently may become more important than how long it takes to perform this task.
3. Stasis: Having established a new set of routines, patients become reconciled with their loss, while understanding that they may never return to "normal."

Working through each of these stages is necessary for the patient's recovery. Health professionals can help patients acknowledge their loss as well as provide a more hopeful view of the future. In addition, professionals can assist in identifying local resources such as stroke clubs, exercise classes, and family support groups. Participation in these activities can form the basis for the beginning of a resocialization process for the stroke patient and his or her family. ■

Toland BB, Becker G. Re-entering the community. In: Sine R, ed. Management of the stroke patient. Spectrum Press, in press.

Becker G, Kaufman S. Old age, rehabilitation, and research: A review of the issues. The Gerontologist 1988; 23:459–468.

Drs. Becker and Kaufman's "road map" includes a checklist of questions that must be addressed when considering a family's ability to care for an older stroke survivor:

1. **What is the primary caregiver's own health like?**
2. **How much stamina does that person have?**
3. **Will the primary caregiver have to provide physical care or will that kind of care be provided by others?**
4. **What is the family's financial ability?**
5. **Will caring for the patient completely deplete the family's financial resources?**
6. **Would alternatives (e.g., institutionalization) be more expensive?**
7. **Are there social supports available for the primary caregiver? for the patient? What is the nature of this support?**
8. **Can these social supports provide respite for the primary caregiver?**
9. **How much will the caregiver's life be disrupted by taking on these new responsibilities?**
10. **What are the primary caregiver's other responsibilities?**
11. **How determined is the family to bring the patient home?**

In-home therapy assists stroke patients to relearn important skills for independent living.
Photo courtesy of Gary D. Landsman, National Rehabilitation Hospital

Additional Resources

If you want more information about stroke and/or stroke rehabilitation, contact the following organizations:

National Institute on Aging
National Institutes of Health
Federal Building; Room 6C12
Bethesda, MD 20892
(301) 496-1752

National Institute of Neurological Disorders and Stroke
National Institutes of Health
Building 31; Room 8A06
Bethesda, MD 20892
(301) 496-5751

National Institute on Disability and Rehabilitation Research
Department of Education
400 Maryland Ave., SW
Washington, DC 20202
(202) 732-1184

National Stroke Association
300 E. Hampden Ave., Suite 240
Englewood, CO 80110
(303) 762-9922

Living Alone Influences Nutritional Status of Many Older People

Barbara Katzman

Growing older frequently necessitates changes in lifestyle. Many people retire, move to smaller homes in warmer climates, suffer chronic illnesses which often make them dependent on others, or experience the death of a loved one.

One of the most prevalent changes is that many people 65 years of age and older find themselves living alone. In fact, an estimated 30 percent of community-dwelling people in this age group live alone: 41 percent of the women and 15 percent of the men. These percentages are expected to grow as a larger proportion of the total population live into old age.

Living alone imposes several fundamental changes in lifestyle. Perhaps one of the most common is that often there is no one with whom to plan, prepare, and share meals. Further, there is no one to ensure that the individual will eat foods that will adequately nourish and energize.

In a study relating living arrangements to an older person's diet—and the first-ever study of dietary practices of people over 75 years of age who live alone—investigators found a correlation between living alone and a poor quality diet.

NIA grantee Dr. Maradee Davis and colleagues at the University of California, San Francisco, examined data from the Nationwide Food Consumption Survey conducted by the U.S. Department of Agriculture. Respondents included nearly 4,500 people age 55 years and older who were either living alone or with a spouse. Analysis included such factors as economic status, employment, health, body mass, caloric intake, and vitamin supplementation. Additionally, daily logs recorded participants' diets over a period of three consecutive days.

For the purposes of this study, the definition of dietary quality comes from the Recommended Dietary Allowances (RDA) established by the Food and Nutrition Board of the National Academy of Sciences. A poor diet consists of less than two-thirds of the RDA for at least five of the nine nutrients selected for study. The nutrients considered were vitamins A, C, B1, B2, B6, B12, and the minerals calcium, iron, and magnesium. Generally, these nutrients are underconsumed by older adults.

In all, sixteen percent of the participants consumed poor diets. Generally, however, men living alone were more often at risk of poor nutrition than men living with a spouse. The percentage of men living alone with poor quality diets increased from 16 percent in the age group 55 to 64 to 25 percent in the age group 75+. The pattern was less consistent for women. Inexplicably, the only women living alone who consumed a poor quality diet were those between the ages of 55 and 64. For women 75+ years of age, slightly more of those living with a spouse than those living alone had poor quality diets. Overall, when considering both types of living arrangements, a higher proportion of women than men had unsatisfactory diets.

Davis found that calorie intake is the single most important variable to explain the link between living arrangement and diet. Persons living alone consume less food; many even skip meals. With the decrease of food consumption, the choices a person makes as to what to eat become more important for compliance with suggested nutritional requirements. An individual's goal should be the selection of foods rich in nutrients, moderate calories, and avoidance of foods loaded with calories but with little nutritional value.

Investigators speculate that the reasons why older people shun good nutritional habits may vary with gender. On the one hand, men living alone are at particular risk because they are traditionally unaccustomed to planning, shopping, and preparing for meals. On the other hand, women are at risk of nutritional deficiencies because they may be less motivated to prepare meals when there is no one with whom to share them.

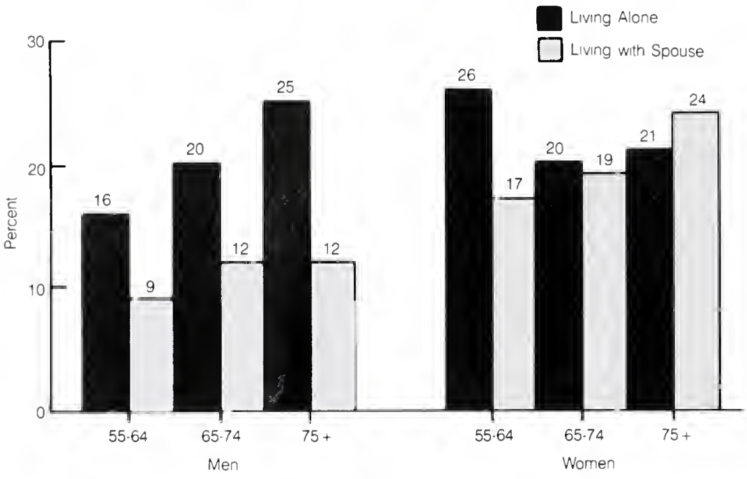
Juana Aguilar is 102 years old. Women generally require fewer calories than men yet basically have similar requirements for most nutrients.

Women generally require fewer calories than men yet basically have similar requirements for most nutrients. Therefore, women must be more selective in choosing foods in order to receive the recommended amounts of vitamins and minerals without adding empty calories. The study suggests that burning off calories with exercise enables older individuals, particularly women, to eat more food containing required nutrients, thereby increasing the overall quality of a diet.

Dr. Davis found that economic status did not influence the association between living arrangement and dietary quality. Older men living alone spent more money on food than those living with a spouse yet more of them had poor quality diets.

Poor diet can be a result of existing social conditions. Some older people, particularly those living alone, may be lonely, socially isolated, and physically and/or emotionally unable to shop for and prepare meals. The impact of these factors should not be underrated. Many people use mealtimes as a social activity. How-

Percentage of Older U.S. Adults with Poor Quality Diets by Age, Sex and Living Arrangement Group



Data from Nationwide Food Consumption Survey 1977-78

ever, widowed persons may not seek the social interaction that encourages eating three well-balanced meals a day. Many people do not enjoy eating alone, won't spend the time cooking for themselves, and prefer to eat quick, often unnourishing snacks.

This study suggests the importance of educational programs to help solitary older people improve their nutritional well-being. This is a valuable target group for local and state support programs to reinforce sound educational concepts in nutrition. Health promotion programs attract mostly women so the importance of programs that instruct newly widowed men to plan and prepare meals, and encourage interaction among peers, would be a most valuable tool in maintaining adequate nutrition among this group of people. Older men who live alone are at special risk yet are an underserved population that requires special efforts. Attempts to bring people together for meals and other activities may be extremely important to the physical, psychological, and social well-being of older individuals.

It is important to increase our understanding of what induces a person to adhere to sound nutritional practices. Whether such decisions derive from personality traits or life style patterns, or both, is not clear. More research is urgently needed to be able to ensure a healthier diet for single older people. ■

Davis MA, Murphy SP, et al. Living arrangements and eating behaviors of older adults in the United States. Journal of Gerontology 1988; 43:S96–98.

Dr. Maradee A. Davis is the recipient of the National Institute on Aging's Merit Award. The primary purpose of this award is to provide long-term stable support to investigators whose research competence and productivity are distinctly superior.

Selection criteria for Merit Awards include: at least two previous grants totaling not less than 7 years of support, research consistent with NIA priorities, emphasis on the field of aging in previous and current research, and an investigator recognized as a leader in his/her field.

In reviewing survey data, NIA-supported researchers found a relationship between poor quality diets and living alone.

Eat Less and Live Longer?

Patricia Cunningham

The search for ways to extend healthy life is not new. Through the ages, people have devoted time, money, and energy to uncovering the mythical fountain of youth. Some scientists now suspect that simply eating less may be part of the solution to this age-old quest for prolonging life.

During the past 50 years, numerous studies on rats and mice have shown the benefits of reducing calories. Indeed, studies on dietary caloric restriction conducted by NIA grantees Drs. Roy Walford and Richard Weindruch* at the University of California at Los Angeles, produced the longest living mice ever reported—53 months (the average life of a mouse is 24–36 months). These rodents also had strong immune systems and reduced cancer rates. Likewise, several studies on life extension and caloric restriction by Dr. Edward Masoro and his associates at the University of Texas Health Center found fewer signs of early aging in mice who ate less.

Against this background of positive data on the effects of caloric modification in spiders, fruit flies, guppies, and rodents, investigators questioned whether longer living species would benefit as well. What remains undetermined is whether dietary restriction actually slows the aging process or if the carefully planned experimental diets contained fewer foods known to contribute to illnesses such as heart disease. To find answers to these and other questions, NIA scientists Drs. George Roth, Donald Ingram, and Richard Cutler began to examine the effects of dietary restriction on selected primates. The study is examining the effects on health and longevity of a 30 percent reduction in calories in the diets of 60 rhesus monkeys and 33 squirrel monkeys.

A major concern in setting up the study was to provide a nutritionally adequate diet for each animal. The objective was to achieve undernutrition without malnutrition—to feed experimental groups nearly a third less food than the control groups without harming their general health. Groups of monkeys were introduced to the dietary restriction regime

An adult male rhesus monkey.

gradually over a three-month period. Scientists formulated each diet to ensure that it contained the required concentration of vitamins and minerals. They then monitored diets carefully to avoid error resulting from the untidy feeding behaviors of monkeys in captivity.

Scientists divided the all-male animals into three age groups—juvenile, young adult, and aged—to determine if any potential benefit of caloric restriction is linked to age. Control and experimental squirrel monkey subgroups included both juvenile and young adults for purposes of long-term study. Older animals received only the control diet for cross-sectional age comparisons. All three age groups of rhesus monkeys were divided into control and experimental sub-groups. At the initiation of the study, control and experimental groups were matched on the basis of body weight as well as age.

Except for a few individually housed aged rhesus monkeys who were exceptionally large, all animals had cage mates of matching species, age, and diet. Housing provided for interconnecting cages with sliding partitions to allow for interaction between animals. The investigators were particularly sensitive to the psychological well-being of the monkeys. Thus, adequate exercise space, social contact, and toys for entertainment were all essential factors in maintaining the most comfortable research conditions. The sole purpose of isolation during feeding time was to enable scientists to control the food intake of the animals.

Findings from the recently completed first year of this project include information on body weight, blood chemistry, and cell counts as they relate to aging processes. Each animal received non-invasive physiological and biochemical tests. From analysis of the blood chemistry data, monkeys suffered no harm to their health. Both rhesus and squirrel monkeys remained healthy throughout the year and continued to gain weight, although groups on the restricted diet gained weight at a slower rate. All monkeys continued to show normal growth patterns. As yet, there have been no age-related changes to favor one diet over the other.

Investigators hope that these tests will contribute to our knowledge of normal aging processes. These studies might also pinpoint some of the common chronic conditions that might benefit from caloric modification. Previous studies on mice have shown, for example, that reducing calories affects the immune system by altering both the thymus gland and the number of disease-fighting cells. Researchers agree that if dietary restriction benefits primates it could be an important step to prolonging active life expectancy in humans.

Dietary caloric restriction has been the single most consistent method of extending the life span of rats and mice; however, it is not yet known if this finding will apply to other primates, most particularly to humans. ■

An adult male squirrel monkey.

Photos courtesy of Bernadette M. Marriott. They may not be reproduced without permission from Dr. Marriott, the Johns Hopkins University.

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* Dr. Weindruch is currently a health scientist administrator at NIA.

NIA News Notes

Fiber Found to Reduce Risk Factors for Disease

Jan Ehrman

Increasing the amount of foods in your diet that are high in crude fiber may reduce risk factors for disease. This is the conclusion from a retrospective analysis of food intake recorded by subjects in a 17-year study of healthy individuals conducted by scientists at the NIA-supported Gerontology Research Center (GRC) in Baltimore.

For some time, the medical community and much of the general public have been aware of the health benefits of fiber. Dietary patterns reflect the fact that fibrous foods have become a focus in the diets of many health-conscious consumers. Accumulating evidence indicates that a high fiber diet can reduce symptoms associated with specific gastrointestinal problems including constipation, irritable bowel syndrome, and diverticulosis. Fiber shortens the transit time of foods, thereby offsetting the changes in motility often seen with age. Also, many experts claim that eating foods high in insoluble fiber lowers the risk for developing certain cancers, primarily cancers of the colon and rectum.

In addition, reports from the medical literature indicate that increasing dietary fiber may have a role in helping to lower high blood cholesterol and may thus reduce the risk for coronary heart disease (CHD). For some individuals, certain types of fiber may reduce blood lipids (both cholesterol and the fatty substance, triglycerides), lower blood pressure, and improve glucose tolerance (the ability to metabolize sugar). The latter is important since impaired glucose tolerance, *per se*, may heighten the CHD risk, some experts suggest.

However, prior to the GRC investigation, few longitudinal studies examined fiber intake in a relatively healthy population. Such was the focus of the GRC study, directed by NIA nutritionist Dr. Judith Hallfrisch, and reported in a recent issue of the *Journal of Gerontology* (Vol. 43, 1988).

She and her colleagues, Dr. Jordan D. Tobin, Denis C. Muller, and Dr. Reubin Andres, analyzed crude fiber intake in 380 males enrolled in the Institute's Baltimore Longitudinal Study of Aging (BLSA).

At the onset of the study, the subjects ranged in age from their twenties to eighties. These volunteer participants, all healthy, highly motivated individuals from many walks of life, visited the Center for two-and-a-half days of biomedical and behavioral testing every two years. From 1959–1976, investigators collected dietary records as well as valuable information relevant to their lifestyle.

Between visits, participants kept seven-day dietary records, detailing precisely what foods they ate throughout the day. Fiber intake increased as the men aged, regardless of their initial age. During each BLSA stop-over, scientists took measurements of many variables after an overnight fast. Of particular significance to this part of the research, blood pressure, plasma glucose concentrations, serum triglycerides, and cholesterol were analyzed in connection with crude fiber intake. Data analysis from self-reports of food intake showed that the highest level of crude fiber (more than 6 grams per day) was correlated with low levels of a number of risk factors; systolic and diastolic pressures, triglycerides, serum cholesterol, and blood glucose measurements.

Rich Sources of Food Fiber

Breads and cereals	
All Bran	⅓ cup-1 oz
Bran Buds	⅓ cup-1 oz
Bran Chex	⅔ cup-1 oz
Corn Bran	⅔ cup-1 oz
Cracklin' Bran	⅓ cup-1 oz
100% Bran	½ cup-1 oz
Raisin Bran	¾ cup-1 oz
Bran, unsweetened	¼ cup
Wheat germ, toasted, plan	¼ cup-1 oz
Fruits	
Blackberries	½ cup
Dried prunes	3
Legumes (Cooked portions)	
Kidney beans	½ cup
Lima beans	½ cup
Navy beans	½ cup
Pinto beans	½ cup
White beans	½ cup

Source: National Cancer Institute

After adjusting for age, obesity, and caloric intake, men consuming the most fiber showed lower diastolic blood pressures than males taking in the least fiber (only two grams of fiber per day). Serum total cholesterol levels also were somewhat lower among men with the highest fiber intake. Of statistical significance were the differences seen in the serum triglyceride levels. The researchers, after adjusting once again for age, obesity, and calories, found that men consuming more than six grams of crude fiber daily (found in foods like celery, wheat bran, and pears), had considerably lower triglyceride levels than subjects eating less than half that amount of fiber. Finally, another significant finding was that glucose levels after fasting were lower for the participants who consumed the highest fiber intake than for subjects taking the lowest level of fiber.

These research results suggest that healthy individuals consuming diets high in fiber have lower risk factors and, presumably, lower chance for developing heart disease. ■

Researchers Uncover Important Key to Alzheimer's Disease

Marian Emr

Two eminent neuroscientists have combined their research interests and uncovered a critical piece of information on why brain cells die in Alzheimer's disease.

Dr. Carl W. Cotman at the University of California at Irvine and Dr. Dennis J. Selkoe at Harvard Medical School and Brigham and Women's Hospital in Boston, Massachusetts have found that a fragment of the protein in neuritic plaques may possess the ability to regulate growth of nerve cells in the healthy human brain.*

Neuritic plaques, which are dense, insoluble deposits of amyloid protein, are among the major hallmarks of Alzheimer's disease. Until now, scientists have not known what role amyloid protein plays, if any, in healthy brain tissue or why an increasing number of large clusters of amyloid appear in the brains of Alzheimer patients.

Earlier NIA-supported studies revealed that the abnormal amyloid protein is made up of fragments of a larger protein that is normally spread across nerve cell membranes. Scientists also have discovered the approximate location of the gene for the fragment, called the amyloid precursor protein, and have identified the building block amino acids that constitute it.

In the current investigations, Drs. Cotman and Selkoe synthesized the first 28 amino acids of the amyloid protein and tested the effects of this synthetic peptide on nerve cells grown in tissue culture. Nerve cells grown in tissue culture do not survive long, but in the presence of the synthetic peptide, the cells stayed alive for longer periods of time. These results demonstrated that amyloid has a trophic, or growth enhancing, effect on nerve cells.

On the basis of these experiments, Drs. Cotman and Selkoe speculate that plaque formation in Alzheimer's disease may signal the nerve cells' attempt to mount a defense against the degenerative process and to compensate for the damage that occurs as the disease progresses. The investigators also speculate that events in the early stages of Alzheimer's disease may lead to the production of an abnormal amyloid protein that malfunctions and contributes to the progress of the disease.

Scientists at the NIA are hopeful about the results of this work, as well as recent research on nerve growth factor, one of several known trophic factors that enhances the survival of injured nerve cells. As investigators learn more about how and why cells die in Alzheimer's disease, it may become possible to slow the progression of the disease using nerve growth factor or similar substances.

Prior to this latest research, Dr. Selkoe was widely recognized for his research on amyloid protein as well as on the proteins that form the characteristic neurofibrillary tangles of Alzheimer's disease. Dr. Cotman distinguished himself with his pioneering studies of synaptic plasticity, the ability of damaged or diseased nerve cells to repair themselves. Both of the investigators have received long-term research support from the NIA and are recent recipients of NIA grants for Leadership and Excellence in Alzheimer's Disease (LEAD). ■

Latest Findings on Urinary Incontinence: More is Known But Problems Remain

Karen McCrory Pocinki

The latest findings on urinary incontinence in adults indicate that although much is already known more research is needed on this important cause of disability and dependency in the elderly.

Urinary incontinence, the involuntary loss of urine so severe as to have social and/or hygienic consequences, is a major clinical problem. Although new diagnostic tests have been developed, well-defined guidelines are still needed for their application, and opinions differ widely concerning the best treatment for many specific forms of the disorder. Knowledge of the causes and consequences of incontinence has increased; however, the number of patients with urinary incontinence who are not treated successfully remains surprisingly high.

In the fall of 1988, the National Institutes of Health held a Consensus Development Conference on Urinary Incontinence in Adults to resolve issues regarding the incidence, causes, and treatment of incontinence. Based on the scientific data presented, a consensus panel, drawn from the medical profession, basic sciences, and general public, produced a consensus statement. Following are the panel's findings.

Urinary incontinence is very common among older Americans and is epidemic in nursing homes. At least 10 million adult Americans suffer from incontinence, including approximately 15 to 30 percent of community-dwelling older people and at least one-half of the 1.5 million nursing home residents in this country.

Urinary incontinence is not part of normal aging. However, age-related changes in lower urinary tract function predispose the older person to incontinence in the face of additional anatomic or physiologic insults to the urinary tract or systemic disturbances. Often, incontinence is due to multiple interacting conditions.

More than half of the people with urinary incontinence in the community have not consulted a physician about the problem. Many of these individuals turn prematurely to the use of absorbent materials without having their difficulty properly diagnosed and treated. In addition, many physicians fail to recognize the clinical impact of urinary incontinence in nursing homes, and as a result, very few nursing home residents with incontinence have any type of diagnostic evaluation.

Every person with urinary incontinence is entitled to evaluation and consideration for treatment. Evaluation must be tailored to the individual, taking into account clinical, cognitive, functional, and residential status in addition to the potential for correcting the problem. A thorough history, careful physical examination, and provoked full-bladder stress test are recommended. Based on the findings of this evaluation, a decision for treatment or more definitive testing is made, taking into consideration the type and degree of incontinence.

Contrary to public opinion, most cases of urinary incontinence can be cured or improved. Behavioral techniques, pharmacologic therapy, and surgery may be used to treat individuals with incontinence. As a general rule, the least invasive or dangerous procedures should be tried first. For patients who have not been treated successfully, management plans must be developed to maximize their well-being.

There is an urgent need to educate professionals and paraprofessionals about urinary incontinence. Information on incontinence should be included in undergraduate and graduate professional training. In addition, continuing education courses focusing on the types of incontinence and appropriate diagnostic procedures and treatments should be offered.

Directions for future research include studies of the causes of urinary incontinence and its occurrence in specific populations, ways to prevent incontinence, and new treatments for this condition.

Free, single copies of the complete NIH Consensus Statement on Urinary Incontinence in Adults may be obtained from the Office of Medical Applications of Research, Building 1, Room 216, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892. ■

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*The results of this research, funded by the National Institute on Aging (NIA), appear in the March 17, 1989 issue of *Science* magazine, "Amyloid B Protein Enhances the Survival of Hippocampal Neurons *in Vitro*," by Janet S. Whitson, Dennis J. Selkoe, and Carl W. Cotman.

NIA News Notes

Sleep Study Opens Eyes to New Thinking

Barbara Katzman

As people age they often experience changes in sleeping patterns. Complaints may range from insomnia to frequent arousals from sleep to extreme daytime sleepiness. One sleep disorder, sleep apnea, has been estimated to affect some 5 million people age 65 and older. Sleep apnea is the periodic cessation of breathing during sleep, with each episode lasting at least 10 seconds and occurring at least 5, to as many as 12, times per hour. The episode ends when the person wakes up.

Admittedly, sleep apnea is not a household phrase. However, the condition is worrisome to scientists studying sleep and to physicians who specialize in sleep disorders. They believe that sleep apnea causes serious health problems for many people and should be treated. It can result in daytime sleepiness that may affect memory, attention span and a person's ability to drive a car or operate potentially dangerous machinery. If left untreated, sleep apnea can cause lowered blood oxygen, cardiac arrhythmia and, in rare cases, a fatal heart attack. A recent NIA-supported study, however, challenges whether sleep apnea is as prevalent a problem to the older population as previously suggested. Many more older people than necessary may be considered potential risks for cardiovascular disease.

Dr. Allan Pack and colleagues at the University of Pennsylvania studied a healthy, active group of people who had passed their 64th birthday. Subjects were divided into two groups, those who had been diagnosed as having sleep apnea and those who had not. Each subject spent two nights in the sleep laboratory for evaluation. Every participant was monitored for total sleep time, number of apneas per hour, number of arousals from sleep, length of apnea episodes, and supply of oxygen during various stages of sleep. Subjects underwent neuropsychological testing both before and after sleep tests. Cardiovascular examination included blood pressure checks.

Results of the study showed no significant difference between the two groups in total sleep time or in nighttime awakenings. This older group of people did not have a history of increased cardiovascular disease or hypertension, both associated with sleep-related respiratory disturbances in younger people. Similarly, there were no significant differences between the two groups in neuropsychological tests.

The criteria for diagnosis of sleep apnea have been developed in studies of younger persons with sleep disorders. The application of these criteria to healthy older people, however, remains controversial. Dr. Pack and his colleagues found no evidence for increased hypertension, cardiovascular disease, or memory loss in older people with apnea. What the study did find was that older people with a diagnosis of sleep apnea tended to experience excessive daytime sleepiness.

Many people experience symptoms of sleep apnea. They include loud and intermittent snoring, excessive body movements and gasping for breath during sleep, and extreme daytime sleepiness. Overweight men are the most prone to this condition.

Obviously, symptoms of sleep apnea are common. Proper diagnosis is extremely important, however, because treatment for sleep disorders vary so drastically. Sleeping pills to treat insomnia may actually be quite harmful to people with sleep apnea because they could extend apnea episodes resulting in even lower levels of blood oxygen.

Perhaps, as the study suggests, the definition of sleep apnea should be adjusted to accommodate healthy older people. Since therapeutic intervention carries with it a degree of risk, more careful consideration of those risks versus the consequences of the sleep disturbance should be thoroughly assessed. ■

Pack AI, Knight H et al. Clinical significance of sleep apnea in the elderly. American Review of Respiratory Diseases 1987; 136: 845–850.

Age Pages

NIA's Age Pages provide a quick, practical look at some of the health topics that interest older people. Selected titles are available in Chinese (C) or Spanish (S).

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